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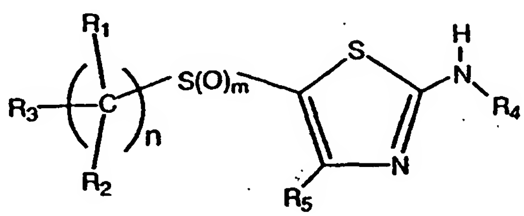
# (54) Title: AMINOTHIAZOLE INHIBITORS OF CYCLIN DEPENDENT KINASES



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(57) Abstract: Compounds of formula (I) and pharmaceutically acceptable salts thereof. As used in formula (I), and throughout the specification, the symbols have the following meanings: $R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl; $R_3$ is aryl or heteroaryl, $R_4$ has various meanings; $R_5$ is hydrogen or alkyl; m is an integer of 0 to 2; and n is an integer of 1 to 3. The compounds of formula (I) are protein kinase inhibitors and are useful in the treatment and prevention of proliferative diseases, for example, cancer, inflammation and arthritis. They may also be useful in the treatment of neurodegenerative diseases such as Alzheimer's diseases cardiovascular diseases, viral diseases and fungal diseases.

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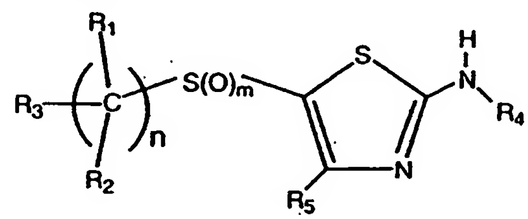
# AMINOTHIAZOLE INHIBITORS OF CYCLIN DEPENDENT KINASES

## Brief Description of the Invention

The present invention is directed to compounds of the formula



(I)

and pharmaceutically acceptable salts thereof. As used in formula I, and throughout the specification, the symbols have the following meanings:

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is aryl or heteroaryl

$R_4$ is alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

$SO_2$-cycloalkyl, $SO_2$-aryl, $SO_2$-alkyl-cycloalkyl, $SO_2$-alkyl-aryl, $SO_2$-heteroaryl, $SO_2$-alkyl-heteroaryl, $SO_2$-heterocycloalkyl, $SO_2$-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl,

## Description of the Invention

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

It should be noted that any heteroatom with unsatisfied valances is assumed to have the hydrogen atom to satisfy the valances.

Carboxylate anion refers to a negatively charged group $-COO^{-}$.

The term "alkyl" or "alk" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 12 carbon atoms unless otherwise defined. An alkyl group is an optionally substituted straight, branched or cyclic saturated hydrocarbon group. When substituted, alkyl groups may be substituted with up to four substituent groups, R as defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group". Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. Exemplary substituents may include but are not limited to one or more of the following groups: halo (such as F, Cl, Br, I), haloalkyl (such as $CCl_3$ or $CF_3$), alkoxy, alkylthio, hydroxy, carboxy (-COOH), alkyloxycarbonyl (-C(O)R), alkylcarbonyloxy (-OCOR), amino ($-NH_2$), carbamoyl (-NHCOOR- or -OCONHR-), urea (-NHCONHR-) or thiol (-SH). Alkyl

groups as defined may also comprise one or more carbon to carbon double bonds or one or more carbon to carbon triple bonds.

The term “alkenyl” refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon double bond.

The term “alkynyl” refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond.

Cycloalkyl is a specie of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings. Exemplary unsubstituted such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, etc. Exemplary substituents include one or more of the following groups: halogen, alkyl, alkoxy, alkyl hydroxy, amino, nitro, cyano, thiol and/or alkylthio.

The terms "alkoxy" or "alkylthio", as used herein, denote an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The term "alkyloxycarbonyl", as used herein, denotes an alkoxy group bonded through a carbonyl group. An alkoxycarbonyl radical is represented by the formula: -C(O)OR, where the R group is a straight or branched $C_{1-6}$ alkyl group.

The term "alkylcarbonyl" refers to an alkyl group bonded through a carbonyl group.

The term "alkylcarbonyloxy", as used herein, denotes an alkylcarbonyl group which is bonded through an oxygen linkage.

The term “arylalkyl”, as used herein, denotes an aromatic ring bonded to an alkyl group as described above.

The term "aryl" refers to monocyclic or bicyclic aromatic rings, e.g. phenyl, substituted phenyl and the like, as well as groups which are fused, e.g., napthyl, phenanthrenyl and the like. An aryl group thus contains at

least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Aryl groups may optionally be substituted with one or more groups including, but not limited to halogen, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, nitro, trifluoromethyl, amino, cycloalkyl, cyano, alkyl $S(O)_m$ (m=O, 1, 2), or thiol.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S, or N, in which a carbon or nitrogen atom is the point of attachment, and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms, said heteroaryl group being optionally substituted as described herein. Exemplary heteroaryl groups include the following: thienyl, furyl, pyrrolyl, pyridinyl, imidazolyl, pyrrolidinyl, piperidinyl, thiazolyl, oxazolyl, triazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyrazinyl, pyridazinyl, pyrimidinal, triazinylazepinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzoxadiazolyl, benzofurazanyl and tetrahydropyranyl. Exemplary substituents include one or more of the following: halogen, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, trifluoromethyl, cycloalkyl, nitro, cyano, amino, alkyl$S(O)_m$ (m=0, 1, 2), or thiol.

The term "heteroarylium" refers to heteroaryl groups bearing a quaternary nitrogen atom and thus a positive charge.

The term "heterocycloalkyl" refers to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms.

The term "quaternary nitrogen" refers to a tetravalent positively charged nitrogen atom including, e.g. the positively charged nitrogen in a tetraalkylammonium group (e.g. tetramethylammonium, N-methylpyridinium), the positively charged nitrogen in protonated ammonium species (e.g. trimethylhydroammonium, N-hydropyridinium), the positively charged nitrogen in amine N-oxides (e.g. N-methyl-morpholine-N-oxide, pyridine -N-oxide), and the positively charged nitrogen in an N-amino-ammonium group (e.g. N-aminopyridinium).

The term "heteroatom" means O, S or N, selected on an independent basis.

The term "halogen" or "halo" refers to chlorine, bromine, fluorine or iodine.

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

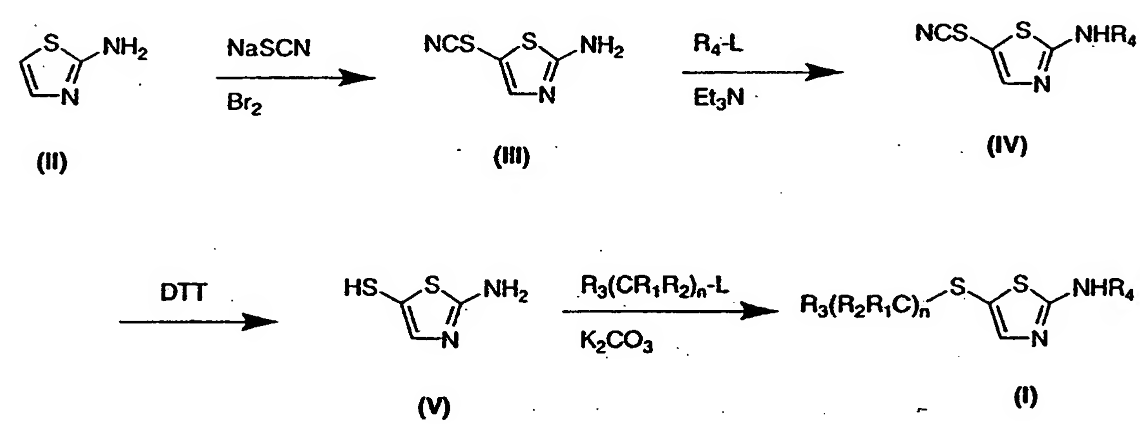
Suitable examples of salts of the compounds according to the invention with inorganic or organic acids are hydrochloride, hydrobromide, sulfate, phosphate. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of the compounds according to the invention embraces all possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified

activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

It should be understood that solvates (e.g., hydrates) of the compounds of formula I are also within the scope of the present invention. Methods of solvation are generally known in the art. Accordingly, the compounds of the instant invention may be in the free or hydrate form, and may be obtained by methods exemplified by the following schemes.

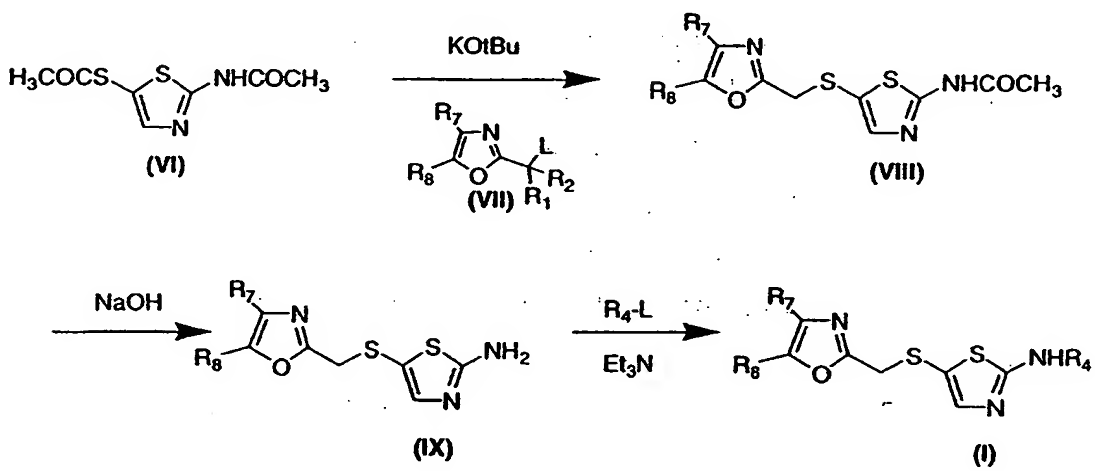
**Scheme 1**




As illustrated in Scheme 1, compounds of formula I where X is S are prepared by reacting 2-aminothiazole (II) with bromine in the presence of sodium or potassium thiocyanate to obtain a thiocyanated aminothiazole, specifically 5-thiocyanatoaminothiazole (III). Compound III is then reacted with $R_4$-L, where L is a leaving group such as a halogen, in the presence of a base such as triethylamine to provide a 5-thiocyanatothiazole intermediate (IV), where $R_4$ is as defined in the specification. The intermediate (IV) is then reduced to a thiol (V) using

reducing agents such as dithiothreitol (DTT), sodium borohydride, zinc or other known reducing agents. Compound (V) is then reacted with alkyl, aryl or heteroaryl halides, such as $R_3$ $(CR_1R_2)_n$-L, where L is a leaving group such as a halogen, in the presence of a base such as potassium carbonate to obtain compounds of formula I. The steps of reducing the thiocyanothiazole intermediate (IV) to the thiol (V), and the reaction of the reduced thiol (V) to provide compounds of formula I where X is S, may be carried out sequentially without purification.

**Scheme 2**



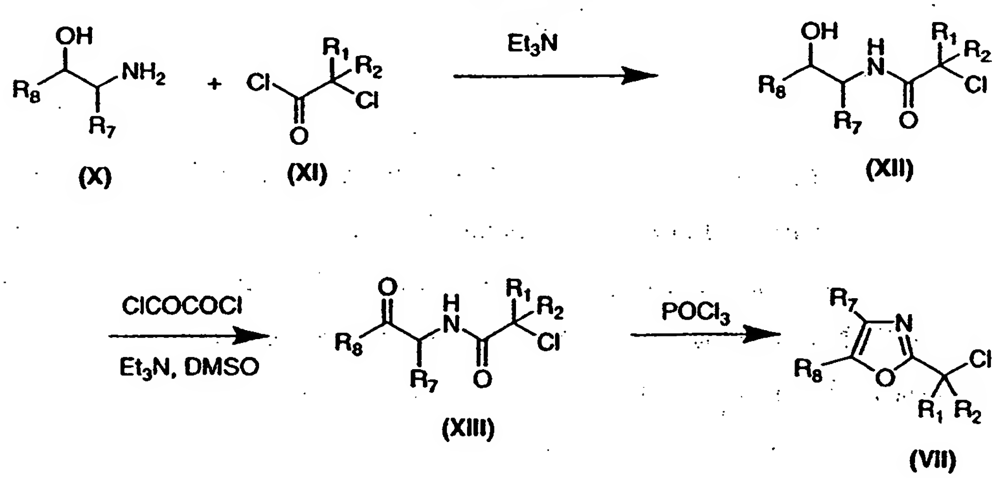

In Scheme 2, 5-thioacetyl-2-acetylaminothiazole of structure VI is reacted with an alkoxide such as potassium t-butoxide in alcohol or THF solvent and the resulting thiol is reacted *in situ* with a group of formula $R_3(CR_1R_2)_n$-L (where L is a leaving group, such as a halogen) such as 2-halomethyloxazole (VII) to provide a compound such as formula VIII, wherein $R_1$ and $R_2$ are hydrogen, and $R_6$ is acetyl. The 2-halomethyloxazole compounds of formula VII may be prepared using

several synthetic routes known in the art. *Chem. Pharm. Bull.* 30, 1865 (1982); *Bull. Chem. Soc. Japan* (52, 3597 (1979); *JCS Chem. Comm.* 322 (1981); *Comprehensive Heterocyclic Chemistry*, vol. 6, 177, edited by A. Katritzky and C.W. Rees, Pergamon Press (1984).

Compounds of formula VIII (a compound of formula I where $R_4$ is acetyl and X is sulfur) can be hydrolyzed in the presence of a base such as sodium hydroxide to provide a compound of formula IX. A compound of formula IX may then be reacted with $R_4$-L, in the presence of a base such as triethylamine, where L is a leaving group such as a halogen, to give compounds of formula I where X is sulfur. In this manner, compounds of formula IX, which is a compound of formula I where $R_4$ is hydrogen, can be treated with agents such as isothiocyanates, halides, acyl halides, chloroformates, isocyanates or sulfonyl chlorides to provide thioureas, amines, amides, carbamates, ureas or sulfonamides. The procedures in Scheme 2 specifically illustrate a methyloxazole group, but are general for all $R_3(CR_1R_2)_n$- groups specified by formula I.

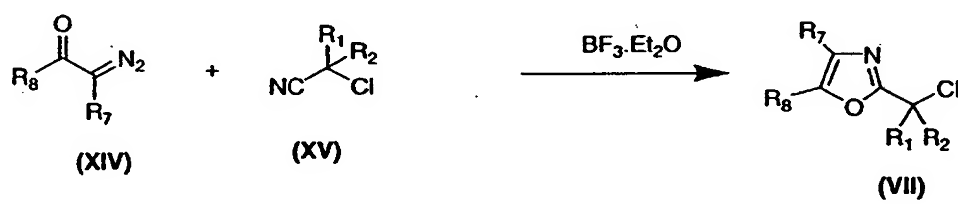
Alternatively, compounds of formula VII, where L is bromine, may be prepared by halogenation of 2-methyloxazole using N-bromosuccinimide in the presence of dibenzoylperoxide.

**Scheme 3**



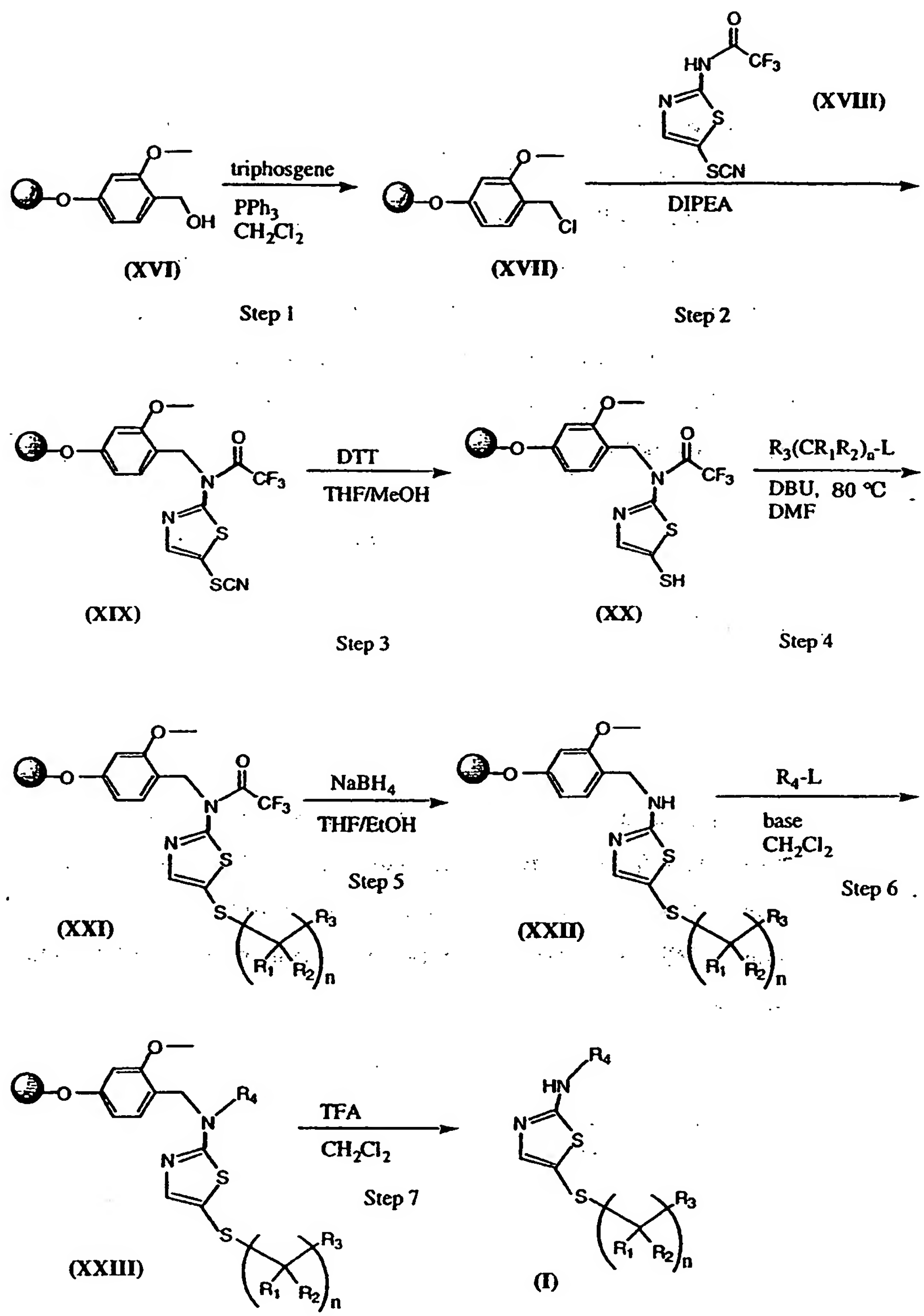
Scheme 3 illustrates an alternative method of preparing compound VII, which is a compound of formula $R_3(CR_1R_2)_n$-L where L is chlorine and n is the integer 1. In this scheme, compound VII is prepared by the reaction of a compound of formula X and formula XI in the presence of a base such as triethylamine to provide compounds of formula XII. Compound XII may be oxidized by an oxidant such as oxalylchloride/DMSO in the presence of a base such as triethylamine to provide a compound of formula XIII which may be cyclized by an agent such as phosphorous oxychloride to provide compounds of formula VII, wherein L is chlorine. Alternatively, compounds of formula XIII may be prepared by reaction of the amino ketone correponding to X with an acid chloride such as XI.

**Scheme 4**




Compounds of formula VII, where L is chlorine, may also be prepared from the reaction of diazoketones as illustrated by formula XIV in Scheme 4 with chloronitriles, such as indicated by formula XV, in the presence of $BF_3$ etherate to provide compounds of formula VII, wherein L is chlorine.

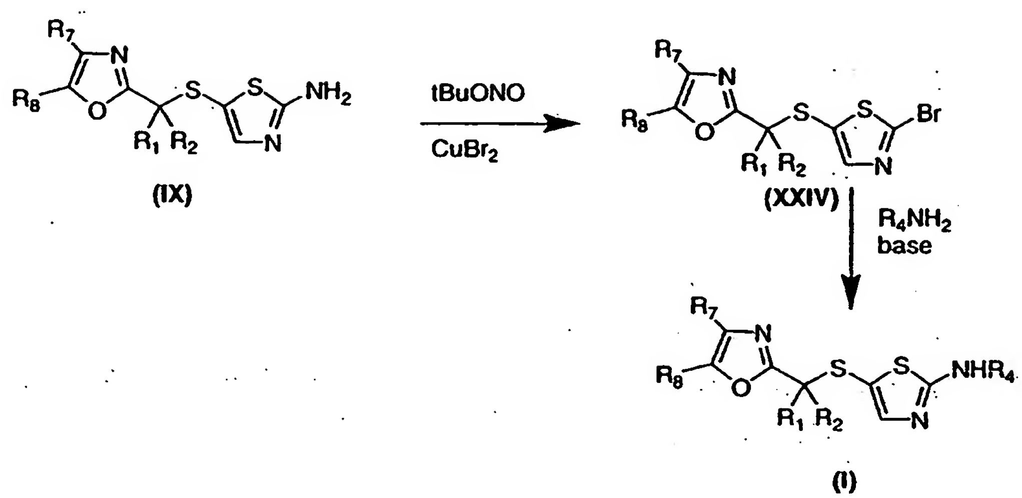
## Scheme 5


(XVIII)
triphosgene
PPh3
CH2Cl2
DIPEA
(XVI)
(XVII)
Step 1
Step 2
DTT
THF/MeOH
R3(CR1R2)n-L
DBU, 80 °C
DMF
(XIX)
(XX)
Step 3
Step 4
NaBH4
THF/EtOH
Step 5
R4-L
base
CH2Cl2
Step 6
(XXI)
(XXII)
TFA
CH2Cl2
Step 7
(XXIII)
(I)

In Scheme 5, starting compound XVI denotes a resin-bound benzyl alcohol support used for solid phase synthesis which is prepared from a Merrifield resin denoted as , and 2-methoxy-4-hydroxybenzaldehyde, followed by reduction with reducing agents such as $NaBH_4$. In step 1, starting compound XVI is treated with triphosgene and triphenylphosphine ($PPh_3$) in dichloromethane to give the chlorobenzyl resin of formula XVII. In step 2, a thiocyanato trifluoroacetamide (XVIII) is alkylated with the resin-bound benzyl chloride (XVII) in the presence of diisopropylethylamine (DIPEA) to form a resin-bound thiocyanate (XIX). The thiocyanato trifluoroacetamide compound of formula XVII is prepared by reacting 5-thiocyanatoaminothiazole of formula III (Scheme I) with trifluoroacetic anhydride using a base such as 2,6-lutidine.

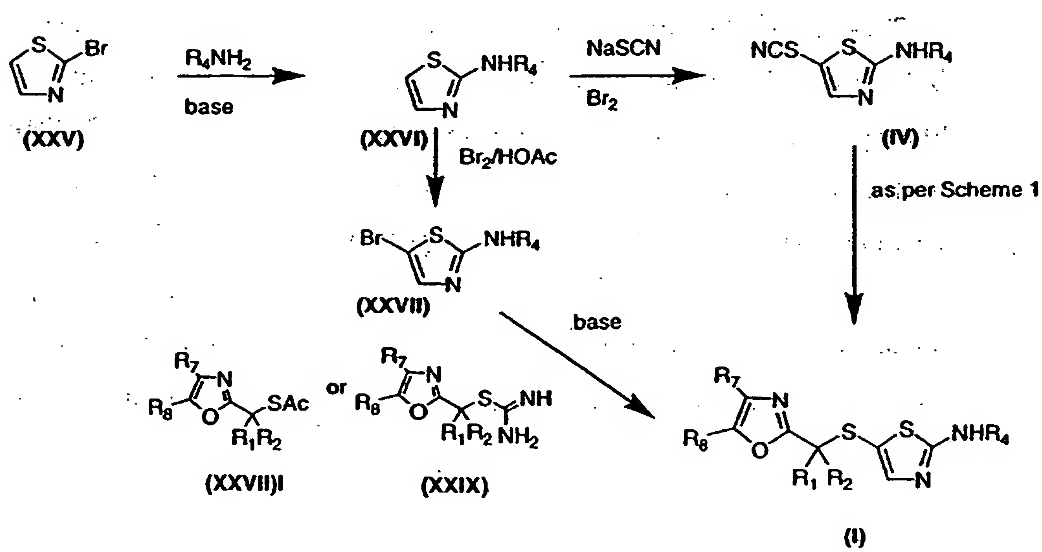
The resin-bound thiocyanate (XIX) is then reduced to a resin-bound thiol (XX) in step 3 with reducing agent such as dithiothreitol (DTT) in tetrahydrofuran (THF) and methanol. The resulting resin-bound thiol (XX) is reacted with $R_3(CR_1R_2)_n$-L, where L is a leaving group, in the presence of a base such as 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) at 80 °C in dimethylformamide (DMF) to form compounds of formula XXI (step 4). Deprotection of the trifluoroacetyl group of compound XXI is performed in step 5 using sodium borohydride to provide a compound of formula XXII. In step 6, the deprotected compound XXII is reacted with $R_6X$, where X is a leaving group, in the presence of a base such as diisopropylethylamine to provide compounds of formula XXIII. The product is then cleaved from the solid phase resin in step 7 with trifluoroacetic acid (TFA) to give compounds of formula I where X is sulfur. Compounds of formula I where X is $S(O)_m$ and m is 1 or 2 may be prepared from compounds of formula I where m is 0 by oxidation with an oxidant such as sodium periodate, meta-chloroperbenzoic acid, or oxone.

## Scheme 6




Scheme 6 illustrates the preparation of compounds of formula I from a 2-bromo thiazole XXIV. A compound of formula IX is reacted with a diazotizing agent such as tBuONO in the presence of copper bromide to provide the exemplary 2-bromo thiazole of formula XXIV. Compound XXIV may then be reacted with a compound of formula $R_4NH_2$, with or without an added base, to provide compounds of formula I.

## Scheme 7



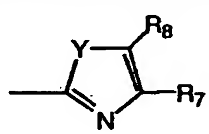
Compounds of formula I may also be prepared starting from 2-bromothiazole XXV by reaction with a compound of formula $R_4NH_2$, with or without an added base, to provide a compound of formula XXVI. The compound of formula XXVI may be reacted with a thiocyanating agent such as sodium thiocyanate in the presence of bromine to provide a compound of formula IV, that may then be converted to a compound of formula I as described in Scheme 1. Alternatively, the compound of formula XXVI may be treated with a brominating agent such as bromine in acetic acid to generate a compound XXVII. Compounds of formula XXVII may be reacted with either XXVIII or XXIX (themselves available from a compound of formula VII) in the presence of base to provide compounds of formula I.

The starting compounds of Schemes 1-7 are commercially available or may be prepared by methods known to one of ordinary skill in the art.

All compounds of formula I may be prepared by modification of the procedures described herein.

The preferred compounds of formula I are those where:

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 


wherein Y is oxygen, sulfur or $NR_9$;

$R_4$ is alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl,

CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

$SO_2$-cycloalkyl, $SO_2$-aryl, $SO_2$-alkyl-cycloalkyl, $SO_2$-alkyl-aryl, $SO_2$-heteroaryl, $SO_2$-alkyl-heteroaryl, $SO_2$-heterocycloalkyl, $SO_2$-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

C($NNO_2$)NH-alkyl, C($NNO_2$)NH-cycloalkyl, C($NNO_2$)NH-aryl, C($NNO_2$)NH-alkyl-cycloalkyl, C($NNO_2$)NH-alkyl-aryl, C($NNO_2$)NH-heteroaryl, C($NNO_2$)NH-alkyl-heteroaryl, C($NNO_2$)NH-heterocyloalkyl, C($NNO_2$)NH-alkyl-heterocycloalkyl; or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

C($NOR_6$)NH-alkyl, C($NOR_6$)NH-cycloalkyl, C($NOR_6$)NH-aryl, C($NOR_6$)NH-alkyl-cycloalkyl, C($NOR_6$)NH-alkyl-aryl, C($NOR_6$)NH-heteroaryl, C($NOR_6$)NH-alkyl-heteroaryl, C($NOR_6$)NH-heterocylcoalkyl, C($NOR_6$)NH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen; and

$R_6$ is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

$R_7$ and $R_8$ are independently hydrogen, alkyl, cycloalkyl, aryl, alkylcycloalkyl, alkylaryl, heteroaryl, alkylheteroaryl, heterocycloalkyl, alkylheterocycloalkyl or halogen;

$R_9$ is H or alkyl;

m is the integer 0; and

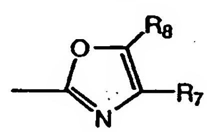
n is the integer 1.

The most preferred compounds of formula I are those where:

$R_1$ is hydrogen;

$R_2$ is hydrogen, fluorine or alkyl;

$R_3$ is a substituted oxazole having the configuration:



;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-cycloalkyl, CO-alkyl-heteroaryl, CO-alkyl-heteroalkyl, CO-alkyl-heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl;

$R_5$ is hydrogen;

$R_7$ is hydrogen;

$R_8$ is an alkyl group, such as tert-butyl;

m is the integer 0; and

n is the integer 1.

The compounds according to the invention have pharmacological properties; in particular, the compounds of formula I are inhibitors of protein kinases such as the cyclin dependent kinases (cdks), for example, cdc2 (cdk1), cdk2, and cdk4. The novel compounds of formula I are expected to be useful in the therapy of proliferative diseases such as

cancer, autoimmune diseases, viral diseases, fungal diseases, neurodegenerative disorders and cardiovascular disease.

More specifically, the compounds of formula I are useful in the treatment of a variety of cancers, including (but not limited to) the following:

-carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

-hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

-hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;

-tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and

-other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of cdks in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary

fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

Compounds of formula I may also be useful in the treatment of Alzheimer's disease, as suggested by the recent finding that cdk5 is involved in the phosphorylation of tau protein (*J. Biochem*, 117, 741-749 (1995)).

Compounds of formula I may induce or inhibit apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of formula I, as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned hereinabove), viral infections (including but not limited to herpevirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of formula I, as inhibitors of the cdks, can modulate the level of cellular RNA and DNA synthesis. These agents would therefore

be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of formula I may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of formula I may also be useful in inhibiting tumor angiogenesis and metastasis.

Compounds of formula I may also act as inhibitors of other protein kinases, e.g., protein kinase C, her2, raf l, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, weel kinase, Src, Abl and thus be effective in the treatment of diseases associated with other protein kinases.

The compounds of this invention may also be useful in combination (administered together or sequentially) with known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methoxtrexate. Compounds of formula I may also be useful in combination with modulators of p53 transactivation.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent or treatment within its approved dosage range. For example, the cdc2 inhibitor olomucine has been found to act synergistically with known cytotoxic agents in inducing

apoptosis (*J. Cell Sci.*, 108, 2897 (1995)). Compounds of formula I may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of formula I may be administered either prior to or after administration of the known anticancer or cytotoxic agent. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor flavopiridol is affected by the sequence of administration with anticancer agents. *Cancer Research*, 57, 3375 (1997).

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and their salts. The compounds of examples 1 to 14 exhibited cdc2/cyclin B1 kinase activity with $IC_{50}$ values less than 50 μM. The compounds of examples 1 to 14 exhibited cdk2/cyclin E kinase activity with $IC_{50}$ values less than 50 μM. The compounds of examples 1 to 14 exhibited cdk4/cyclin D1 kinase activity with $IC_{50}$ values less than 50 μM.

## <u>cdc2/cyclin B1 Kinase Assay</u>

cdc2/cyclin B1 kinase activity was determined by monitoring the incorporation of $^{32}P$ into histone H1. The reaction consisted of 50 ng baculovirus expressed GST-cdc2, 75 ng baculovirus expressed GST-cyclin B1, 1 μg histone HI (Boehringer Mannheim), 0.2 mCi of $^{32}P$ g-ATP and 25 mM ATP in kinase buffer (50 mM Tris, pH 8.0, 10 mM $MgCl_2$, 1 mM EGTA, 0.5 mM DTT). The reaction was incubated at 30°C for 30 minutes and then stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15% and incubated on ice for 20 minutes. The reaction was harvested onto GF/C unifilter plates (Packard) using a Packard Filtermate Universal harvester, and the filters were counted on a Packard TopCount 96-well liquid scintillation counter (Marshak, D.R.,

Vanderberg, M.T., Bae, Y.S., Yu, I.J., *J. of Cellular Biochemistry*, 45, 391-400 (1991), incorporated by reference herein).

**cdk2/cyclin E Kinase Assay**

cdk2/cyclin E kinase activity was determined by monitoring the incorporation of $^{32}P$ into the retinoblastoma protein. The reaction consisted of 2.5 ng baculovirus expressed GST-cdk2/cyclin E, 500 ng bacterially produced GST-retinoblastoma protein (aa 776-928), 0.2 mCi $^{32}P$ g-ATP and 25 mM ATP in kinase buffer (50 mM Hepes, pH 8.0, 10 mM $MgCl_2$, 5 mM EGTA, 2 mM DTT). The reaction was incubated at 30°C for 30 minutes and then stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15% and incubated on ice for 20 minutes. The reaction was harvested onto GF/C unifilter plates (Packard) using a Packard Filtermate Universal harvester, and the filters were counted on a Packard TopCount 96-well liquid scintillation counter.

**cdk 4/cyclin D1 Kinase Activity**

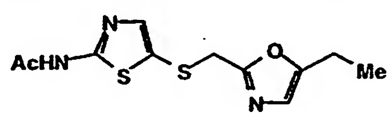
cdk4/cyclin D1 kinase activity was determined by monitoring the incorporation of $^{32}P$ in to the retinoblastoma protein. The reaction consisted of 165 ng baculovirus expressed as GST-cdk4, 282 ng bacterially expressed as S-tag cyclin D1, 500 ng bacterially produced GST-retinoblastoma protein (aa 776-928), 0.2μCi $^{32}P$ γ-ATP and 25 μM ATP in kinase buffer (50 mM Hepes, pH 8.0, 10 mM $MgCl_2$, 5 mM EGTA, 2 mM DTT). The reaction was incubated at 30°C for 1 hour and then stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15% and incubated on ice for 20 minutes. The reaction was harvested onto GF/C unifilter plates (Packard) using a Packard Filtermate Universal harvester, and the filters were counted on a Packard TopCount 96-well liquid scintillation counter (Coleman, K.G., Wautlet, B.S., Morissey, D, Mulheron, J.G., Sedman, S., Brinkley, P., Price, S., Wedster, K.R. (1997). Identification of CDK4 Sequences involved in cyclin D, and p16 binding. *J. Biol. Chem.* 272,30:18869-18874, incorporated by reference herein).

Further subject matter of the invention also includes pharmaceuticals for use as described above including controlling cancer, inflammation and arthritis, which contain at least one compound of the formula I as defined above or at least one of its pharmacologically acceptable acid addition salts, and the use of a compound of the formula I as defined above for the preparation of a pharmaceutical having activity against proliferative diseases as described previously including against cancer, inflammation and/or arthritis.

The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It should be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

## Example 1

**N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide**



**A. Preparation of 1-benzyloxycarbonylamino-2-butanol**

A mixture of 1-amino-2-butanol (5.5 g, 61.8 mmol), benzyl chloroformate (11.5 g, 67.6 mmol) and sodium carbonate (7.16 g, 67.7 mmol) in water (50 mL) was stirred at 0 °C for 3 h. Water (50 mL) was added to the reaction mixture and the product was extracted with methylene chloride (3x20 mL). The methylene chloride extract was dried over $Na_2SO_4$ and concentrated. The residue was passed through a short column ($SiO_2$, hexanes : ethyl acetate /10 : 1; then ethyl acetate) to afford 1-benzyloxycarbonylamino-2-butanol (13.9 g, 100%) as a liquid.

$^1$H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.45 (s, 1 H), 5.06 (s, 2 H), 3.57 (s, 1 H), 3.31 (m, 1 H), 3.04 (m, 1 H), 2.91 (m, 1 H), 1.43 (m, 2 H), 0.91 (t, J = 7.6 Hz, 3 H).

**B. Preparation of 1-benzyloxycarbonylamino-2-butanone**

To methylene chloride (60 mL) at -78 °C under argon was added oxalyl chloride (37 mL of 2 M solution in methylene chloride, 74 mmol), followed by DMSO (7.8 g, 100 mmol). The mixture was stirred at -78 °C for 20 min. and to this mixture was added a solution of 1-benzyloxycarbonylamino-2-butanol (13.9 g, 61.8 mmol) in methylene chloride (40 mL). The mixture was stirred at -78 °C for 1 h and triethylamine (21 mL) was added to the mixture. It was warmed to room temperature (rt) and washed successively with 1 N hydrochloric acid and aqueous sodium bicarbonate solution. The methylene chloride solution was dried over $MgSO_4$ and concentrated to afford 1-benzyloxycarbonylamino-2-butanone (11.2 g, 82%) as a solid, which was enough pure for the next reaction.

$^1$H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 5.50 (s, 1 H), 5.06 (s, 2 H), 4.07 (s, 2 H), 2.43 (q, J = 7.6 Hz, 2 H), 1.06 (t, J = 7.6 Hz, 3 H).

**C. Preparation of 1-amino-2-butanone**

A solution of 1-benzyloxycarbonylamino-2-butanone (9.30 mg, 42 mmol) in ethanol (50 mL) and 1 N hydrochloric acid (46 mL) was stirred under hydrogen atmosphere in the presence of Pd/C (1.5 g, 10%) at rt for 4 h. The mixture was filtered through a celite bed and the filtrate solution was concentrated. The residue was triturated with ethyl ether to afford 1-amino-2-butanone (5.3 g, 102%) as a hydrochloride salt.

$^1$H NMR ($CD_3OD$) δ 3.97 (s, 2 H), 2.60 (q, J = 7.6 Hz, 2 H), 1.08 (t, J = 7.6

Hz,

3 H).

**D. Preparation of 2-amino-5-thiocyanatothiazole**

2-Aminothiazole (41g, 410 mM) and sodium thiocyanate (60 g, 740 mM, dried in a vacuum oven at 130 °C overnight) was dissolved in 450 mL of anhydrous methanol and the solution was cooled in a cold water bath. Here was added bromine (23 mL, 445 mM) dropwise with good stirring. After the addition it was stirred for 4 h at rt. To the mixture 500 mL of water was added and it was stirred for 5 minutes, filtered through a celite bed and washed the bed with water. The pH of the filtrate solution was about 1. Most of the methanol was removed under the reduced pressure and pH of the solution was adjusted to about 7 by adding aq. sodium carbonate slowly with stirring. The precipitated solid was filtered and washed with water to obtain 37 g (57%) of the dark brown colored desired product after drying, mp 140-143 °C.

$^1$H NMR ($CD_3OD$) δ 7.33 (s, 1H); MS ($CI/NH_3$) m/e 179 $(M+Na)^+$, 158$(M+H)^+$.

**E. Preparation of of 2-acetylamino-5-thiocyanatothiazole**

To a mixture of 2-amino-5-thiocyanatothiazole (15.7 g, 0.1 mol) and pyridine (12 g, 0.15 mol) in methylene chloride (100 mL) was added acetic anhydride (1.2 g, 0.12 mol) at rt. The mixture was stirred at rt for 6 h. The mixture was concentrated to dryness and to the residue MeOH (50 mL) was added. The precipitates were collected and washed with water. The solid was dried and recrystallized from MeOH to afford 2-acetylamino-5-thiocyanatothiazole (15.2 g, 76%) as a solid, mp 212 °C.

$^1$H NMR ($CD_3OD$) δ 7.79 (s, 1H), 2.23 (s, 3 H).

**F. Preparation of [[2-(acetylamino)-5-thiazolyl]thio]acetic acid 1,1-dimethylethyl ester**

To a mixture of 2-acetamino-5-thiocyanatothiazole (5.97 g, 30 mmol) in MeOH (360 mL) under argon was added dithiothreitol (9.26 g, 60

mmol) at rt. The mixture was stirred at rt for 2 h and it was concentrated to afford a reduced solid product. This solid product was dissolved in DMF (30 mL) and to this solution were added tert-butyl bromoacetate (5.85 g, 30 mmol) and potassium carbonate (5.0 g, 36 mmol). The mixture was stirred at rt for 2 h and water (200 mL) was added to the mixture. The precipitates were collected, washed with water and dried. The solid was dissolved in methylene chloride (100 mL) and MeOH (10 mL) and filtered through a silica gel pad. The filtrate solution was concentrated to afford the desired product (7.5 g, 87%) as a solid, mp 162-163 °C.

$^1$H NMR ($CDCl_3$) δ 12.2 (s, 1 H), 7.48 (s, 1 H), 3.37 (s, 2 H), 2.32 (s, 3 H), 1.45 (s, 9 H); MS m/e 289 $(M+H)^+$, 287 $(M-H)^-$.

HPLC (Column: YMC S3 ODS 4.6x150mm; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10% MeOH-90% water-0.2% $H_3PO_4$; Solvent B: 90% MeOH-10% Water-0.2% $H_3PO_4$; UV: 220 nm): retention time 6.44 min.

G. **Preparation of [[2-(acetylamino)-5-thiazolyl]thio]acetic acid**

A solution of [[2-(acetylamino)-5-thiazolyl]thio]acetic acid 1,1-dimethylethyl ester (4.32 g, 15 mmol) in methylene chloride (30 mL) and trifluoroacetic acid (20 mL) was stirred at rt overnight and concentrated *in vacuo*. To the residue was added ethyl ether (50 mL). The precipitated solid was collected, washed with ethyl ether and dried to afford the desired product (3.38 g, 97%) as a solid, mp 210 °C.

$^1$H NMR ($CD_3OD$) δ 7.48 (s, 1 H), 3.47 (s, 2 H), 2.20 (s, 3 H) ppm; MS m/e 231$(M-H)^-$; HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10% MeOH-90% water-0.2%$H_3PO_4$; Solvent B: 90% MeOH-10% Water-0.2% $H_3PO_4$; UV: 254 nm): retention time 4.32 min.

### H. Preparation of [[2-(acetylamino)-5-thiazolyl]thio]-N-(2-oxobutyl)acetamide

A mixture of [[2-(acetylamino)-5-thiazolyl]thio]acetic acid (9.0 g, 38.8 mmol), HOBT (5.94 g, 38.8 mmol) and ethyldimethylaminopropylcarbodiimide hydrochloride salt (11.16 g, 58.2 mmol) in DMF (50 mL) was stirred at 0 °C for 0.5 h. To this mixture was added 1-amino-2-butanone hydrochloride (5.27 g, 42.7 mmol) followed by triethylamine (15 mL, 107.5 mmol). The mixture was stirred at 0 °C for 0.5 h and at rt for 1 h. Water (200 mL) was added to the mixture and the product was extracted with methylene chloride containing 10% MeOH (5x100 mL). The methylene chloride extract was dried over $Na_2SO_4$ and concentrated.

The residue was triturated with water and the precipitated solid product was collected by filtration. It was dried to obtain the desired product (10.5 g, 90%), mp 195-196 °C.

$^1H$ NMR ($CDCl_3$) δ 7.53 (s, 1 H), 4.14 (s, 2 H), 3.46 (s, 2 H), 2.50 (q, J = 7.6 Hz, 2 H), 2.25 (s, 3 H), 1.12 (t, J = 7.6 Hz, 3 H); MS m/e 302 $(M+H)^+$. HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10%MeOH-90%water-0.2%$H_3PO_4$; Solvent B: 90%MeOH-10%Water-0.2%$H_3PO_4$; UV: 254 nm): retention time 4.36 min.

### I. Preparation of N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide

To a solution of [[2-(acetylamino)-5-thiazolyl]thio]-N-(2-oxobutyl)acetamide (10.5 g, 34.8 mmol) in acetic anhydride (100 mL) was added conc. sulfuric acid (10 mL). The mixture was stirred at 55-60 °C for 2 h and sodium acetate (15 g, 0.18 mol) was added to the mixture. The mixture was concentrated *in vacuo*. To the residue was added cold water (100 mL). The precipitated solid was collected, washed with water and dried. It was purified by a flash column chromatography ($SiO_2$; methylene chloride :

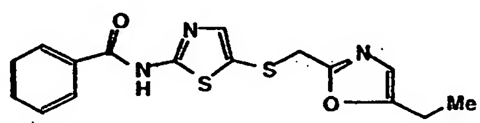
MeOH / 100 : 5) to afford N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide (4.2 g, 43%) as a solid, mp 147-148 °C.

$^1$H NMR ($CDCl_3$) δ 12.47 (s, 1 H), 7.29 (s, 1 H), 6.61 (s, 1 H), 3.91 (s, 2 H), 2.64 (q, J = 7.6 Hz, 2 H), 2.25 (s, 3 H), 1.21 (t, J = 7.6 Hz, 3 H) ppm; MS m/e 284 $(M+H)^+$;

HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10%MeOH-90%water-0.2%$H_3PO_4$; Solvent B: 90%MeOH-10%Water-0.2%$H_3PO_4$; UV: 254 nm): retention time 6.50 min.

## Example 2

**N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzamide**



### A. Preparation of 2-amino-5-[[(5-ethyl-2-oxazolyl)methyl]thio]-thiazole

A solution of N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide (1.3 g, 4.6 mmol) in 1 N hydrochloric acid (15 mL) was stirred at 80-90 °C for 3 h. It was cooled to rt and the pH of the solution was adjusted to 7 with sodium carbonate. The product was extracted with methylene chloride (3x10 mL). The combined extract was dried over $Na_2SO_4$ and concentrated. The residue was triturated with ethyl ether and the precipitated solid was collected to afford 2-amino-5-[[(5-ethyl-2-oxazolyl)methyl]thio]-thiazole (610 mg, 55%) as a solid, mp 119-120 °C.

$^1$H NMR ($CDCl_3$) δ 6.93 (s, 1 H), 6.61 (s, 1 H), 5.41 (s, 2 H), 3.82 (s, 3 H), 2.62 (q, J =7.6 Hz, 2 H), 1.18 (t, J = 7.6 Hz, 3 H); MS m/e 242 $(M+H)^+$;

HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10%MeOH-90%water-0.2%$H_3PO_4$; Solvent B: 90%MeOH-10%Water-0.2%$H_3PO_4$; UV: 254 nm): retention time 3.96 min.

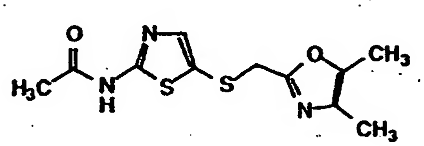
**B. Preparation of N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzamide**

A mixture of 2-amino-5-[[(5-ethyl-2-oxazolyl)methyl]thio]-thiazole (48.2 mg, 0.2 mmol), benzoyl chloride (24.4 mg, 0.21 mmol) and triethylamine (35 mg, 0.35 mmol) in methylene chloride (0.5 mL) was stirred at rt for 10 min. The organic solution was washed with water and concentrated. The residue was purified by a flash column ($SiO_2$; hexanes : ethyl acetate / 2 : 1) to afford N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzamide (41 mg, 59%) as a solid, mp 122-123 °C.

$^1H$ NMR ($CDCl_3$) δ 12.65 (s, 1 H), 7.96 (m, 2 H), 7.61 (m,, 1 H), 7.49 (m, 2 H), 6.88 (s, 1 H), 6.56 (s, 1 H), 3.93 (s, 2 H), 2.61 (q, J = 7.6 Hz, 2 H), 1.20 (t, J = 7.6 Hz, 3 H); MS m/e 346 $(M+H)^+$;
HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10%MeOH-90%water-0.2%$H_3PO_4$; Solvent B: 90%MeOH-10%Water-0.2%$H_3PO_4$; UV: 254 nm): retention time 7.94 min.

## Example 3

**N-[5-[[(4,5-dimethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide**



A. **Preparation of 2-(bromomethyl)-4,5-dimethyloxazole**

A mixture of 2,4,5-trimethyloxazole (0.50 mL, 4.3 mmol), N-bromosuccinimide (0.77 g, 4.3 mmol) and benzoyl peroxide (0.21 g, 0.86 mmol) in carbon tetrachloride (4 mL) was heated at 76° C under nitrogen atm.for 3 hrs. After cooling to rt, the solid was removed by filtration. The filtrate solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and concentrated. The residue was purified by flash column chromatography ($SiO_2$; hexanes:ethyl acetate / 4:1) to afford 2-(bromomethyl)-4,5-dimethyloxazole (64 mg) as an yellow oil.

$^1$H NMR ($CDCl_3$) δ 4.4 (s, 2 H), 2.25 (s, 3 H), 2.05 (s, 3 H).

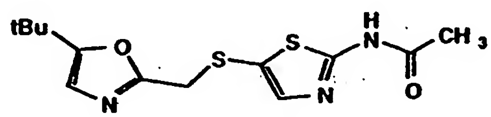
B. **Preparation of N-[5-[[(4,5-dimethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide**

N-[5-(Acetylthio)-2-thiazolyl]acetamide (0.050 g, 0.23 mmol) was dissolved in dry THF (10 ml) and here potassium*tert*-butoxide (1.0 M solution in THF, 0.25 ml, 0.25 mmol) was added to the mixture. The reaction mixture was stirred at rt for 15 min., and 2-(bromomethyl)-4,5-dimethyloxazole (0.064 g, 0.34 mmol) was added to this mixture. The reaction mixture was stirred at rt for 3 h and saturated aqueous $NaHCO_3$ solution (20 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers was concentrated. The residue was purified by flash column chromatography ($SiO_2$; methanol:dichloromethane /1:20) to afford N-[5-[[(4,5-dimethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide (15 mg, 23%) as a yellow solid. $^1$H NMR ($CDCl_3$) δ 11.78 (s, 1 H), 7.38 (s, 1 H), 3.90 (s, 2 H), 2.30 (s, 3H), 2.22 (s 3H), 2.05 (s, 3H); MS m/e 284 $(M+H)^+$; HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 ml/min; solvent system: 0-100% B in 8 min. Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2%

$H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 254 nm): retention time 5.87 min.

## Example 4

## N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide



### A. Preparation of diazomethane

To a mixture of 15 ml of 40% aqueous KOH solution and 50 mL of diethyl ether at 0 °C was added 5 g (68 mmol) of N-methyl-N'-nitro-N-nitrosoguanidine in portions with stirring . The resulting mixture was stirred at 0 °C for 0.5 h. The organic phase was decanted into a dry flask and dried over solid KOH pellets to give 50 mL of diazomethane solution (ca 0.5 M, by titrating with acetic acid).

### B. Preparation of 1-diazo-3,3-dimethyl-2-butanone

To the diazomethane solution at 0 °C was added a solution of 1.23 mL (1.21 g, 10 mmol, Aldrich) of trimethylacetyl chloride in 1 mL of diethyl ether dropwise with stirring. The resulting mixture was kept at 0 °C for 16 h. The solution was sparged with argon to remove the excess diazomethane and diethyl ether was removed under reduced pressure to give 1.33 g (10 mmol, 100%) of crude 1-diazo-3,3-dimethyl-2-butanone as a yellow liquid.

### C. Preparation of 2-chloromethyl-5-t-butyloxazole

To a solution of 2 mL (2.3 g, 16 mmol) of boron trifluoride etherate in 20 mL of chloroacetonitrile at 0 °C was added a solution of 1.33 g (10

mmol) of 1-diazo-3,3-dimethyl-2-butanone in 5 mL of chloroacetonitrile dropwise. The resulting solution was stirred at 0 °C for 0.5 h. The reaction mixture was added to saturated aqueous sodium bicarbonate solution to neutralize the acid and the product was extracted three times with dichloromethane. The combined extracts was dried (sodium sulfate), concentrated and purified by flash column chromatography (Merck silica, 25 x 200 mm, dichloromethane) to give 1.1 g of 2-(chloromethyl)-5-t-butyloxazole as a yellow liquid (6.4 mmol, 64% overall from the acid chloride).

$^1$H NMR δ ($CDCl_3$): 1.30 (s, 9H), 4.58 (s, 2H), 6.68 (s, 1H); MS 174 $(M+H)^+$; TLC: $R_f$ (silica gel, dichloromethane)=0.33;

HPLC: $t_R$ (YMC S-3 ODS 4.6x50mm rapid resolution, 2.5 ml/min, gradient 0-100% B over 8 min, Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 254 nm)= 6.5 min.

D. **Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide**

To a solution of 50 mg (0.23 mmol, Applied Chemical Laboratory) of N-[5-(acetylthio)-2-thiazolyl]acetamide in 10 mL of THF was added 0.25 mL of potassium tert-butoxide solution (1 M solution, 0.25 mmol) at rt under argon. The resulting suspension was stirred for 15 min at rt, then a solution of 59 mg of 2-(chhloromethyl)-5-t-butyloxazole (0.34 mmol) in 1 mL of THF was added. The resulting mixture was stirred at rt for 16 h, concentrated under reduced pressure and purified by flash column chromatography (silica gel, 25 x 200 mm, 1:1 EtOAc/hexanes followed by 100% EtOAc) to give 44 mg (0.14 mmol, 61%) of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide as a white solid.

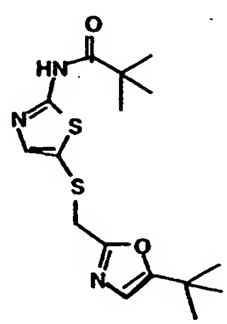
$^1$H NMR δ ($CDCl_3$) 1.27 (s, 9H), 2.27 (s, 3H), 3.95 (s, 2H), 6.59 (s, 1H), 7.31 (s, 1H), 11.03 (broad s, 1H); MS 312 $(M+H)^+$;

TLC: $R_f$ (silica gel, ethyl acetate)=0.53, UV;

HPLC: retention time (YMC S-3 ODS 4.6x50mm rapid resolution; 2.5 ml/min, gradient 0-100%B over 8 min, Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 254 nm)= 6.8 min.

## Example 5

**N-[5-[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl] trimethylacetamide**



### A. Preparation of N-[(5-thiocyanato)-2-thiazolyl] trifluoroacetamide (XVIII)

To a mixture of 5-thiocyanato-2-aminothiazole (30 mmol) and 2,6-lutidine (35 mmol) in tetrahydrofuran (25 mL) and dichloromethane (50 mL) at -78 °C under argon was slowly added trifluoroaceticanhydride (33 mmol). After addition, the mixture was allowed to warm up to rt and stirred overnight. The mixture was diluted with dichloromethane (100 mL), and the organic solution was washed with 5% aqueous citric acid followed by brine, dried over magnesium sulfate and passed through a pad of silica gel. The product containing eluent was concentrated to afford 5.3 g of light brown solid.

$^1H$ -NMR ($CDCl_3$) δ 12.4 (br, 1H), 7.83 (s, 1H).

### B. Preparation of 4-hydroxymethyl-3-methoxyphenyloxy Merrifield resin (XVI)

To the suspension of sodium hydride (11.7 g, 60% in mineral oil, 293 mmol) in dimethylformamide (30 mL) at 0 °C under argon was slowly added a solution of 4-hydroxy-3-methoxybenzyldehyde (44.5 g, 292.5 mmol) in dimethylformamide (100 mL). To the resulting mixture Merrifield resin (1% DVB, from Advanced Chemtech, loading 1.24 mmol/g, 50 g, 62 mmol) and catalytic amount of tetra-n-butylammonium idodide were added, and it was heated at 65 °C for a day. The resin was filtered, washed with water (2x), 50% dimethylformamide in water (3x), dimethylformamide (2x), and methanol (5x), and dried *in vacuo*. The dried resin (15 g) was treated with sodium borohydride (3.4 g, 90 mmol) in tetrahydrofuran (50 mL) and ehthanol (50 mL) overnight. The resin was filtered, washed with 50% dimethylformamide in water (3x), dimethylformamide (2x), methanol (2x), and dichloromethane (5x), and dried *in vacuo*.

### C. Preparation of 4-chloromethyl-3-methoxyphenyloxy Merrifield resin (XVII)

To a solution of triphenylphosphine (17 g, 65 mmol) in dichloromethane (200 mL) at 0 °C was slowly added triphosgene (9.2 g, 31 mmol) portionwise over a period of 30 minutes. After addition, the reaction mixture was stirred at 0 °C for 10 minutes. The solvent was removed *in vacuo* and the residue was redissolved in dichloromethane (200 mL). To this mixture was added 4-hydroxymethyl-3-methoxyphenyloxy Merrifield resin (12 g). The resulting mixture was agitated for 4 h. The resin was washed with dry dichloromethane (6x) and dried *in vacuo*.

**D. Preparation of 4-[N-[(5-thiocyanato)-2-thiazolyltrifluoroacetamido]methyl]-3-methoxyphenyloxy Merrifield resin (XIX)**

A mixture of 4-chloromethyl-3-methoxyphenyloxy Merrifield resin (15g), N-[(5-thiocyanato)-2-thiazolyl]trifluoroacetamide (14 g, 55.3 mmol) and diisopropylethylamine (7.8 mL, 45 mmol) in dimethylformamide (50 mL) and dichloromethane (100 mL) was agitated overnight. The resin was washed with dimethylformamide (2x), methanol (2x), dichloromethane (4x), and dried *in vacuo*.

**E. Preparation of 4-[[N-[(5-mercapto)-2-thiazolyl] trifluoroacetamido]methyl]-3-methoxyphenyloxy Merrifield resin (XX)**

A mixture of 4-[N-[(5-thiocyanato)-2-thiazolyltrifluoroacetamido] methyl]-3-methoxyphenyloxy Merrifield resin (XIX, 18.5 g) and dithiothreitol (12 g, 78 mmol) in tetrahydrofuran (100 mL) and methanol (100 mL) was agitated overnight. The resin was washed with dimethylformamide (2x), methanol (2x), dichloromethane (4x), and dried *in vacuo* and stored under argon at -20 °C.

**F. Preparation of 4-N-[5-[[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trifluoroacetamido]methyl-3-methoxyphenyloxy Merrifield resin (XXI)**

A stream of argon was bubbled through a mixture 4-[[N-[(5-Mercapto)-2-thiazolyl]trifluoroacetamido]methyl]-3-methoxyphenyloxy Merrifield resin (XX, 500 mg), halide (2.0 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 1.5 mmol) in dimethylformamide (3 mL) for 5 min., and the mixture was heated at 80 °C for 2 h. The resin was washed with dimethylformamide (2x), methanol (2x), dichloromethane (4x), and dried *in vacuo*.

**G. Preparation of 4-N-[5-[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]methyl-3-methoxyphenyloxy Merrifield resin (XXII)**

A mixture of 4-N-[5-[[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trifluoroacetamido]methyl-3-methoxyphenyloxy Merrifield resin (XXI, 500 mg) and sodium borohydride (4 mmol) in tetrahydrofuran (2 mL) and ethanol (2 mL) was agitated overnight. The resin was washed with 50% dimethylformamide in water (2x), dimethylformamide (2x), methanol (2x), dichloromethane (4x), and dried *in vacuo*.

**H. Preparation of 4-N-[5-[[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trimethylacetamido]methyl-3-methoxyphenyloxy Merrifield resin (XXIII)**

A mixture of 4-N-[5-[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]methyl-3-methoxyphenyloxy Merrifield resin (XXII, 100 mg), diisopropylethylamine (1.2 mmol) and trimethylacetyl chloride (1 mmol) in dichloromethane (2 mL) in a polypropylene tube fitted with a polyethylene frit and a luer stopcock was agitated overnight. The resin was washed with dimethylformamide (2x), methanol (2x), dichloromethane (4x), and used in the next step without drying.

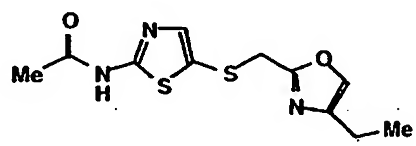
**I. Preparation of N-[5-[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trimethylacetamide**

4-N-[5-[[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trimethylacetamido]methyl-3-methoxyphenyloxy Merrifield resin (XXIII) was treated with 60% trifluoroacetic acid in dichloromethane (2 mL) in a polypropylene tube fitted with a polyethylene frit and a luer stopcock for 4 hours. The solution was decanted to a tube and the resin was washed with dichloromethane. The combined organic solution was concentrated in Speed Vac. The residue was purified by preparative-HPLC to afford 11.3 mg of the desired product.

MS m/e 354 $(M+H)^+$.

## Example 6

## N-[5-[[(4-Ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide



### A. Preparation of 2-(2-chloroacetamido)-1-butanol

To a mixture of 2-amino-1-butanol (5.0 mL, 53 mmol) and triethyl amine (15.0 mL, 111 mmol) in dichloromethane (20 mL) at -70 °C was added chloroacetyl chloride (4.6 mL, 58 mmol) dropwise. The reaction mixture was stirred at -70 °C for 15 min. and then was allowed to warm to rt. It was diluted with EtOAc (50 mL) and the reaction was quenched by adding water (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers was concentrated to afford 2-(2-chloroacetamido)-1-butanol (8.6 g, 98%) as a brown solid.

$^1$H NMR ($CDCl_3$) δ 6.75 (bs, 1 H), 4.10 (s, 2 H), 4.08(dd, 1H), 3.90 (m, 1 H), 3.68 (m, 2H), 2.98(bs, 1H), 1.60(m, 2H), 0.97 (t, 3H).

### B. Preparation of 2-(2-chloroacetamido)-1-butyraldehyde

To a solution of oxalyl chloride (14.5 mL, 29.0 mmol) in dichrolomethane (30 mL) at -78 °C DMSO (2.75 mL, 38.8 mmol) was added dropwise over 5 min.. After stirring for 10 min. at -78 °C, here was added a solution of 2-(2-chloroacetamido)-1-butanol (4.0 g, 24 mmol) in 20 mL of dichrolomethane dropwise over 15 min. The reaction mixture was stirred for 40 min. at -78 °C and here was added triethyl amine (9.4 mL, 68 mmol) dropwise over 5 min. and the reaction mixture was allowed to warm to room temperature and stirred for 2 hrs. The solid was removed by filtration and

washed with EtOAc. The organic phase was washed with 1N HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (1 x 10 mL) and concentrated to afford 2-(2-chloroacetamido)-1-butyraldehyde (3.7 g, 95%) as a brown oil.

$^1H$ NMR ($CDCl_3$) δ 9.60 (s, 1 H), 4.52 (q, 1 H), 4.12(s, 2H), 2.05 (m, 1 H), 1.80 (m, 1H), 0.97 (t, 3H).

**C. Preparation of 2-chloromethy-4-ethyloxazole**

To a solution of 2-(2-chloroacetamido)-1-butyraldehyde (3.7 g, 23 mmol) in toluene (10 mL) was added $POCl_3$ (6.3 mL, 68 mmol). The reaction mixture was heated at 90 °C for 1 h under nitrogen. After cooling the reaction mixture to room temperature it was poured into ice water (10 mL) and the pH of the solution was adjusted to 7 with 5N NaOH. The toluene layer was separated and the aqueous layer was washed with dichloromethane (3 x 20 mL). The combined organic solution was concentrated and distilled to afford 2-chloromethy-4-ethyloxazole (1.1g, 31%) as a colorless liquid.

$^1H$ NMR ($CDCl_3$) δ 7.30 (s, 1H), 4.22 (s, 2 H), 2.50 (q, 2 H), 1.22 (t, 3H).

**D. Preparation of N-[5-[[(4-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide**

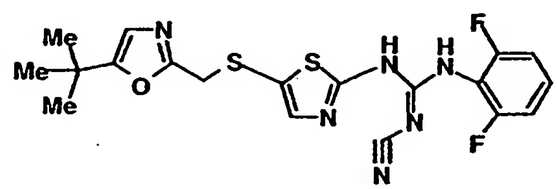
To a solution of 2-acetylamino-5-thiazolylthiol (0.010 g, 0.050 mmol) in dry THF (5 mL) was added potassium *tert*-butoxide (1.0 M solution in THF, 0.060 mL, 0.060 mmol). The reaction mixture was stirred at room temperature for 15 min. and here was added 2-chloromethyl-4-ethyloxazole (0.015 g, 0.10 mmol). After 3 h, saturated aqueous $NaHCO_3$ solution (5 mL) was added to the mixture. The organic layer was separated and the aqueous layer was washed with dichloromethane (3 x 10 mL). The combined organic layers was concentrated. The residue was purified by flash chromatography ($SiO_2$; methanol:dichloromethane /1:20)

to afford N-[5-[[(4-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide (5 mg, 36%) as a white solid.

$^1H$ NMR ($CDCl_3$) δ 11.25 (s, 1 H), 7.34 (s, 1 H), 7.31(s, 1H), 3.95 (s, 2 H), 2.50 (q, 2H), 2.27(s, 3H), 1.19 (t, 3H); MS m/e 284 $(M+H)^+$; HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 ml/min; solvent system: 0-100% B in 8 min. Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 254 nm): retention time 6.14 min.

## Example 7

**Preparation of N-[5-[[(5-*t*-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-N'-cyano-N''-(2,6-difluorophenyl)guanidine.**



A solution of 100 mg of N-[5-[[(5-*t*-Butyl-2-oxazolyl)methyl]thio]-2-aminothiazole and 68 mg of 2,6-difluorophenyl isothiocyanate was heated at 65°C for 16 hours under argon. The solution was evaporated to dryness and the residue purified by flash chromatography to give 91 mg of the intermediate thiourea.

To a solution of 30 mg of N-[5-[[(5-*t*-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-N''-(2,6-difluorophenyl)thiourea, 52 mg of ethyl-3(3-dimethylamino)propyl carbodiimide hydrochloride and 48 µL of diisopropylethylamine in 0.5 mL methylene chloride was added a solution of 29 mg of cyanamide in 0.1 mL tetrahydrofuran. After stirring for 1 hr,

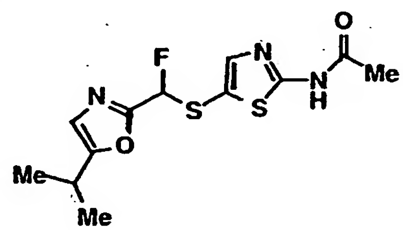
the solvent was removed and the crude material purified by HPLC to give 8 mg of Example 636 compound.

MS: $(M+H)^+$ $449^+$

$^1H$ NMR (400 MHz, $CDCl_3$): d 1.27 (9H, s), 4.19 (2H, s), 6.69 (1H, s), 7.03 (2H, m), 7.35 (1H, m), 8.74 (1H, s).

## Example 8

**Preparation of N-[5-[[(5-isopropyl-2-oxazolyl)fluoromethyl]thio]-2-thiazolyl acetamide.**



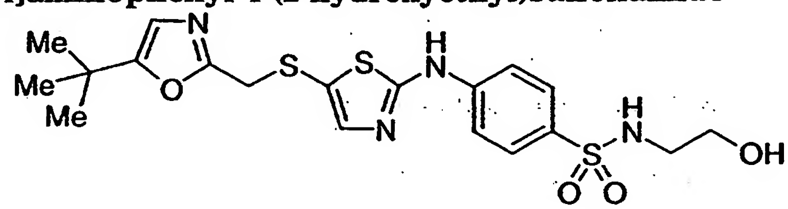
To a stirred mixture of 2-acetamido-5-thiazole thiol acetate (141 mg) in 3 mL of dry THF under argon was added 1N t-BuOK in THF (0.72 mL). This mixture was stirred at room temperature for 25 min, and a solution of 5-isopropyl-(2-(chlorofluoromethyl))oxazole (116 mg) in 2 mL of dry THF was added. The reaction mixture was stirred at 60° C for 18 hr, diluted with 150 mL of EtOAc and washed with saturated $NH_4Cl$ solution (2x25 mL), saturated $NaHCO_3$ solution (1x25 mL) and brine (1x25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give Example 637 compound.

MS: (M+H)+ 316

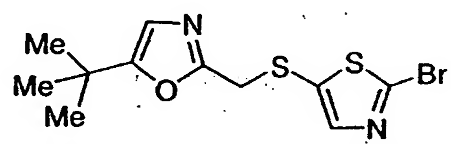
HPLC retention time 3.52 min. (Column: YMC ODS S05 4.6 X 50 mm column, 0% to 100% B gradient in 4 min. Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 220 nM).

## Example 9

**Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]aminophenyl-4-(2-hydroxyethyl)sulfonamide**



**A. Preparation of 5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-bromo thiazole.**



To a solution of $CuBr_2$ (5.14 g in acetonitrile (100 mL) at 0° C was added tBuONO (4 mL, 1.2 eq) followed by 5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]amine (5.2 g). The mixture was stirred at 0° C for one hour, then at room temperature for one hour, ethyl acetate was added and the organic mixture washed with hydrochloric acid (2 X 50 mL), dried over magnesium sulfate, filtered through a pad of silica gel, and concentrated in vacuo. The residue was chromatographed on silica gel to give the bromide as an orange oil (3.9 g).

MS: (M+H)+ 334

HPLC retention time 4.04 min. (Column: YMC ODS S05 4.6 X 50 mm column, 0% to 100% B gradient in 4 min. Solvent A: 10% $CH_3OH$/90%

$H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 220 nM).

**B. Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]aminophenyl-4-(2-hydroxyethyl)sulfonamide**

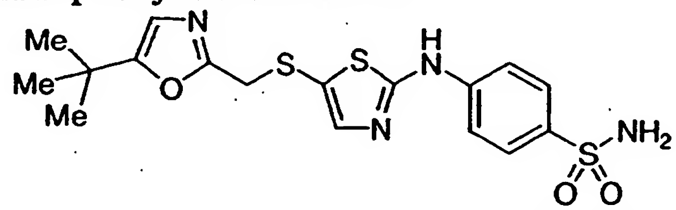
A mixture of the 2-bromothiazole from Part A (0.85 g) in dimethyl acetamide (4 mL) and 4-aminophenyl-N-(2-hydroxyethyl)sulfonamide (2.5 g, 5 eq) was stirred at 145° C for 6 hours, cooled and ethyl acetate (80 mL) was added. The reaction mixture was washed with water (2 X 20 mL), the combined aqueous solution was extracted with ethyl acetate, and the combined organic layers dried over sodium sulfate, evaporated in vacuo, and the residue was chromatographed on silica gel, then purified by reverse phase chromatography to give N-[5-[[(5-t-butyl-2-oxazolyl) methyl]thio]-2-thiazolyl]aminophenyl-4-(2-hydroxyethyl)sulfonamide as a yellow solid (0.61 g).

MS: (M+H)+ 469

HPLC retention time 3.80 min. (Column: YMC ODS S05 4.6 X 50 mm column, 0% to 100% B gradient in 4 min. Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 220 nM).

## Example 10

**Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]aminophenyl-4-sulfonamide**



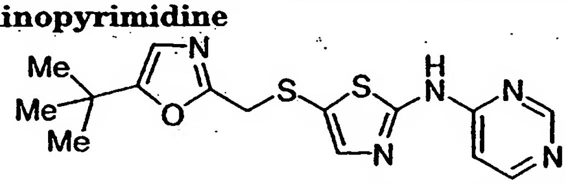
A mixture of the 2-bromothiazole from Example 9, Part A (106 mg) in dimethyl acetamide (0.5 mL) and 4-aminobenzenesulfonamide (275 mg, 5 eq) was stirred at 140° C for 6 hours, cooled and the solvent was removed under reduced pressure to provide a dark red oil which was purified by preparative reverse phase HPLC (YMC S5 ODS) to give N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]aminophenyl-4-sulfonamide (94 mg).

MS: (M+H)+ 425

HPLC retention time 3.74 min. (Column: YMC ODS S05 4.6 X 50 mm column, 0% to 100% B gradient in 4 min. Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 220 nM).

## Example 11

**Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-4-aminopyrimidine**



To a 50 mL single necked flask was added 4-aminopyrimidine (142 mg) in dry tetrahydrofuran (5 mL). A sodium hydride dispersion (60%, 60 mg) was added, followed by heating to 60° C for one hour. The solution of the

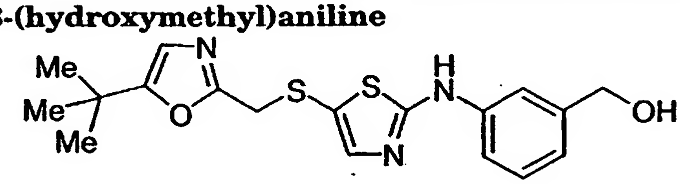
anion was cooled to room temperature and the 2-bromothiazole from Example 9, Part A (100 mg) was added. The reaction was heated for 24 hours at 60° C, cooled to room temparature, quenched with hydrochloric acid and partitioned between water and ethyl acetate (25 mL each). The organic layer was washed with water (2 X 25 mL), brine (25 mL) , dried over sodium sulfate and concentrated in vacuo to give a solid, which was purified by trituration with 1:1 ethyl acetate:hexanes to give N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-4-aminopyrimidine (42 mg).

MS: (M+H)+ 348

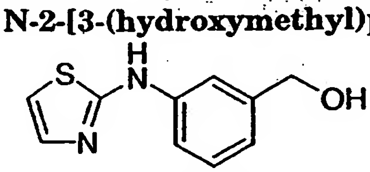
HPLC retention time 3.63 min. (Column: YMC ODS S05 4.6 X 50 mm column, 0% to 100% B gradient in 4 min. Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 220 nM).

## Example 12

**Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-3-(hydroxymethyl)aniline**



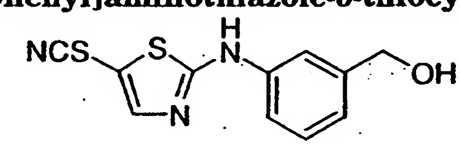
**A. Preparation of N-2-[3-(hydroxymethyl)phenyl]aminothiazole**



To a solution of 3-hydroxymethyl aniline (2.46 g) in dry tetrahydrofuran (50 mL) at –78° C was added methyl lithium-lithium bromide solution in ether (27 mL of 1.5 M solution). The reaction mixture was stirred at –78°

C for 10 minutes, warmed to room temperature for 10 minutes, and then cooled to –78° C and 2-bromothiazole (1.31 g) was added. The reaction mixture was stirred at 0° C for one hour, then at room temperature for 3 hours, quenched by addition of hydrochloric acid (20 mL of 2N solution), concentrated and extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate, concentrated and chromatographed on silica gel to give N-2-[3-(hydroxymethyl)phenyl] aminothiazole (0.68 g).

**B. Preparation of N-2-[3-(hydroxymethyl)phenyl]aminothiazole-5-thiocyanate**



To a cooled solution(ice-salt bath) of the compound of part A (680 mg) and ammonium thiocyanate (500 mg) in methanol (35 mL) was added portionwise bromine (0.21 mL). After disappearance of the bromine color the reaction was concentrated and partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried over sodium sulfate, concentrated and chromatographed on silica gel to give N-2-[3-(hydroxymethyl)phenyl] aminothiazole-5-thiocyanate as a yellow solid (490 mg).

**C. Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-3-(hydroxymethyl)aniline**

To a dark red solution of the thiocyanate of part B (490 mg) in tetrahydrofuran/ethanol was added sodium borohydride portionwise (84

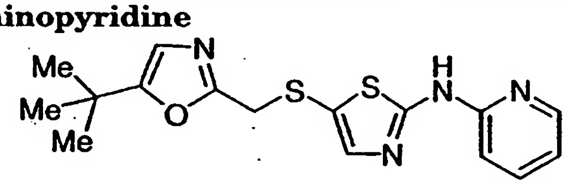
mg). After gas evolution had ceased, acetone (0.65 mL) was added the reaction stirred for 8 minutes, followed by addition of 2-chloromethyl-5-t-butyl-oxazole (Example 5, Part C compound, 0.5 g) and the reaction stirred for one hour at room temperature. The reaction was concentrated, extracted with ethyl acetate, the combined organic extracts dried over sodium sulfate, and filtered through a pad of silica gel to provide the product (0.69 g).

MS: (M+H)+ 376

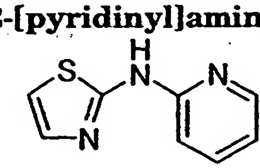
HPLC retention time 3.84 min. (Column: YMC ODS S05 4.6 X 50 mm column, 0% to 100% B gradient in 4 min. Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 220 nM).

## Example 13

**Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-2-aminopyridine**



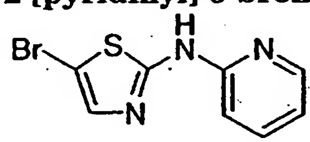
### A. Preparation of N-2-[pyridinyl]aminothiazole



To a suspension of sodium hydride (60% suspension,1.8 g) in tetrahydrofuran (200 mL) was added portionwise 2-aminopyridine (4.23 g), and the mixture was slowly heated to 55° C for 30 minutes. The reaction mixture was then cooled to –10 deg C and a solution of 2-

bromothiazole (2.46 g) in tetrahydrofuran (2 mL) was added dropwise. The reaction mixture was stirred at 55° C for 5 hours, cooled and quenched with hydrochloric acid (2N, 20 mL), concentrated, and ethyl acetate was added. The resulting solid was filtered to give N-2-[pyridinyl]aminothiazole (1.41 g).

**B. Preparation of N-2-[pyridinyl]-5-bromo-aminothiazole**



To a solution of the compound of Part A(0.88 g) in acetic acid(15 mL) was added bromine (0.22 mL in 2 mL acetic acid) dropwise at room temperature. The reaction mixture was stirred at room temperature for 2 hours, the was solvent removed under reduced pressure, and the resulting solid was triturated with ether to provide N-2-[pyridinyl]-5-bromo-aminothiazole (1.6 g) as the hydrobromide salt.

**C. Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-2-aminopyridine**

To a solution of N-2-[pyridinyl]-5-bromo-aminothiazole (8 g) and 2-thioacetyl-5-t-butyl oxazole (8 g) in methanol (500 mL) under argon was added a degassed solution of sodium hydroxide (25 mL of 3 N solution) at room temperature. The reaction mixture was stirred for 20 minutes and then heated to 60° C for one hour, concentrated in vacuo, partitioned between water (125 mL) and ethyl acetate (500 mL) and the aqueous layer was back-extracted (2 X 125 mL) with ethyl acetate. The combined organic layers were washed with brine (25 mL) , dried over sodium

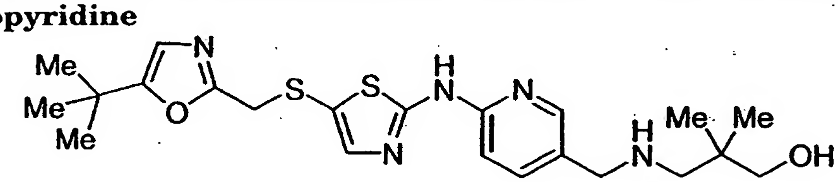
sulfate, filtered through a pad of silica gel,and the solvents removed in vacuo. The solid residue was recrystallized form ethyl acetate to provide N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-2-aminopyridine (7.5 g).

MS: (M+H)+ 347

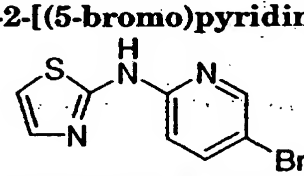
HPLC retention time 4.01 min. (Column: YMC ODS S05 4.6 X 50 mm column, 0% to 100% B gradient in 4 min. Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 220 nM).

## Example 14

**Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-2-[5-[(((3-hydroxy-2,2-dimethyl)propyl)amino)methyl]] aminopyridine**



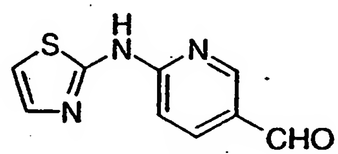
### A. Preparation of N-2-[(5-bromo)pyridinyl]aminothiazole



To a suspension of sodium hydride (60% suspension,5.2 g) in tetrahydrofuran (150 mL) was added portionwise 2-amino-4-bromopyridine (15 g), and the mixture was stirred at room temperature for 15 minutes. 2-Bromothiazole (3.8 mL) was added, and the reaction mixture was stirred at room temperature for one hour and then heated at reflux temperature for 2.5 hours, cooled, quenched with 6% citric acid and

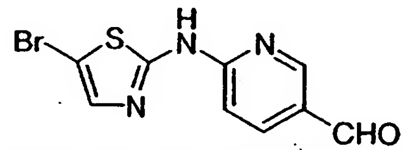
extracted with ethyl acetate (2 X 100 mL). The organic layers were concentrated, dried over magnesium sulfate and the filtrate concentrated in vacuo to give a dark brown residue which was triturated with ether/hexanes to provide N-2-[(5-bromo)pyridinyl]aminothiazole as a yellow solid (8.9 g)

**B. Preparation of N-2-[(5-carboxaldehyde)pyridinyl] aminothiazole**



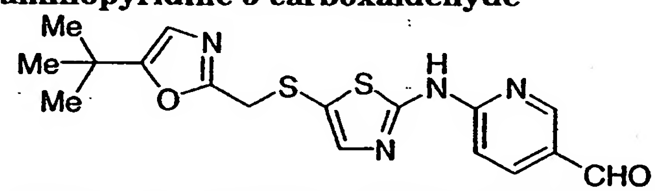
A suspension of the Part A compound (6.4 g) in tetrahydrofuran (300 mL) was heated to reflux to effect dissolution, the reaction mixture was cooled to –70° C and treated with *t*-BuMgCl (13 mL of 2M solution in ether) dropwise over 10 minutes. The temperature was raised to –55° C, and *t*-BuLi (36 mL of 1.7 M solution in hexanes) was added dropwise, and the reaction mixture stirred for 20 minutes. The reaction mixture was then cooled to –70° C and DMF (8 mL) was added, the resulting mixture was stirred at –50° C for one hour and then warmed to 0° C over one hour, quenched with acetic acid (8 mL) and partitioned between ethyl acetate and water (300 mL each). The aqueous layer was back extracted with ethyl acetate (2 X 200 mL) and the combined organic layers dried over magnesium sulfate and concentrated, the solid washed with ethyl acetate and ether, and dried to give N-2-[(5-carboxaldehyde) pyridinyl] aminothiazole (3.15 g).

**C. Preparation of N-2-[(5-carboxaldehyde)pyridinyl]-5-bromo-aminothiazole**



A solution of N-2-[(5-carboxaldehyde) pyridinyl] aminothiazole(0.5 g) in acetic acid (6 mL) and dichloromethane (20 mL) was treated with bromine (0.12 mL) in dichloromethane (3 mL). The reaction mixture was stirred for 30 minutes at room temperature, ether was added, and the resulting precipitate was collected by filtration, washed with ether to give N-2-[(5-carboxaldehyde)pyridinyl]-5-bromo-aminothiazole (0.69 g).

**D. Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-2-aminopyridine-5-carboxaldehyde**



To a solution of the compound of Part C (3.8 g) and 5-t-butyl-2-(S-isothiourea)methyl oxazole (3.06 g) in methanol (300 mL) under nitrogen was added degassed sodium hydroxide (6.4 g of 50% w/w solution). The reaction mixture.was heated at 76° C for 6 hours, the methanol was removed in vacuo, water was added, and the solid was collected by filtration, washed with water and ethyl acetate, and dried to give N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2- thiazolyl]-2-aminopyridine-5-carboxaldehyde (0.53 g). The filtrate was extracted with ethyl acetate (4 X 200 mL), dried over magnesium sulfate, and concentrated in vacuo and

triturated with ether/ethyl acetate to give an additional 2.02 g of the desired compound.

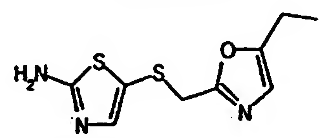
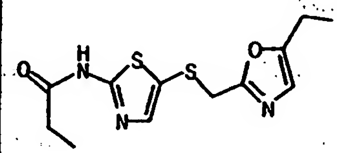
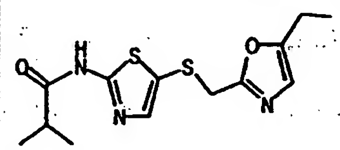
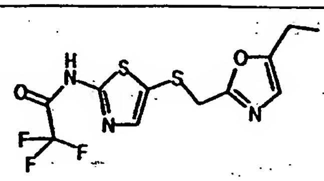
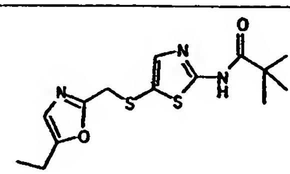
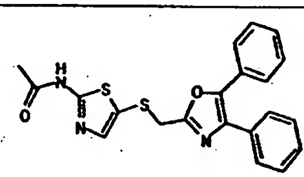
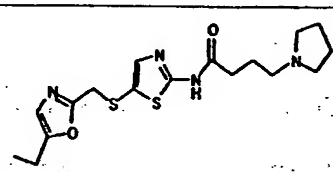
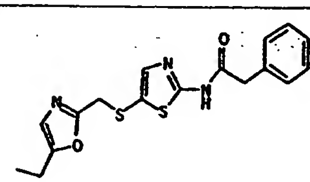
**E. Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-2-[5-[(((3-hydroxy-2,2-dimethyl)propyl)amino)methyl]] aminopyridine**

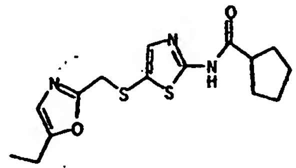
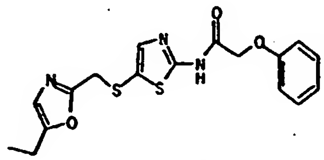
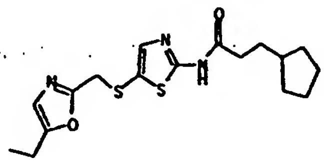
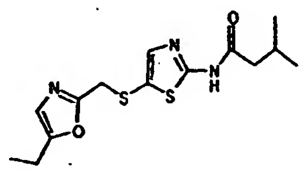
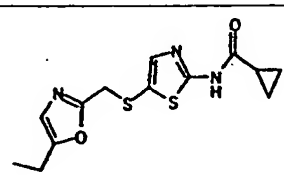
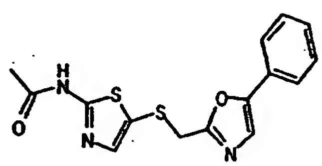
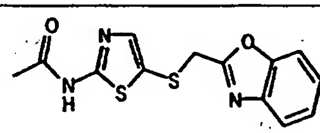
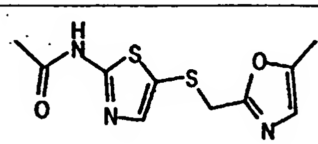
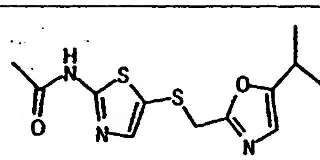
To a solution of the aldehyde of Part D (1.5 g) and 3-amino-2,2-dimethyl propanol (2.06 g) in tetrahydrofuran (100 mL) was added sodium triacetoxyborohydride (6.0 g), followed by acetic acid (5 mL). The reaction mixture was stirred for 30 minutes at room temperature, and the solvents removed in vacuo to give a yellow solid which was purified by column chromatography to give N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-2-[5-[(((3-hydroxy-2,2-dimethyl)propyl)amino)methyl]] aminopyridine (1.08 g).

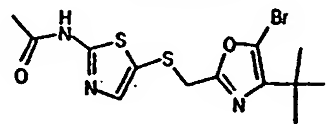
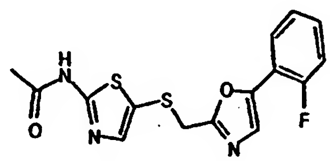
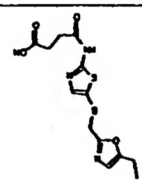
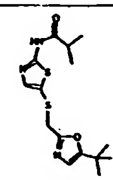
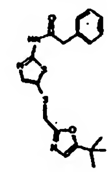
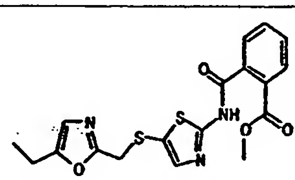
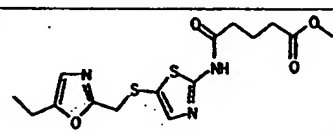
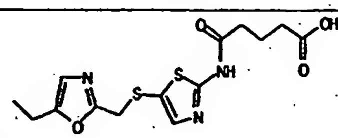
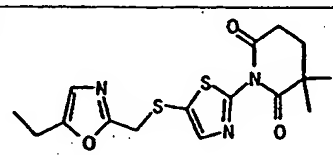
MS: (M+H)+ 462

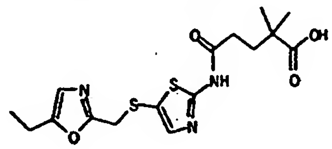
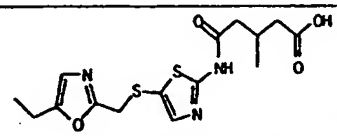
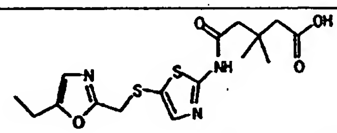
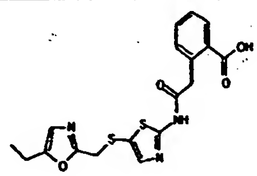
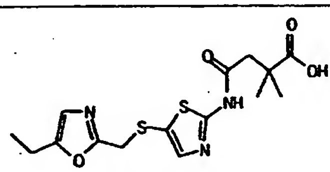
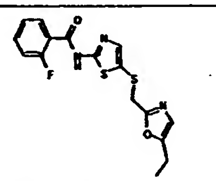
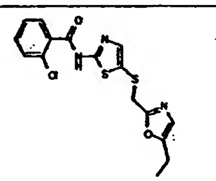
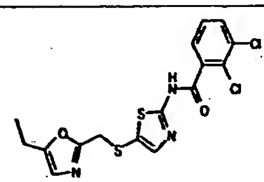
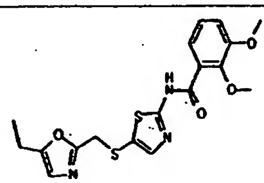
HPLC retention time 3.22 min. (Column: YMC ODS S05 4.6 X 50 mm column, 0% to 100% B gradient in 4 min. Solvent A: 10% $CH_3OH$/90% $H_2O$/0.2% $H_3PO_4$; Solvent B: 90% $CH_3OH$/10% $H_2O$/0.2% $H_3PO_4$; UV: 220 nM).

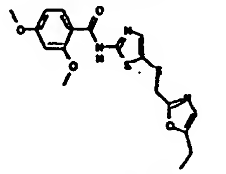
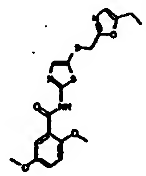
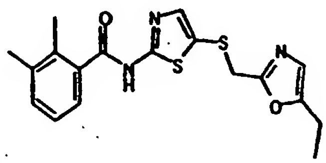
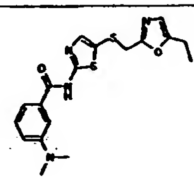
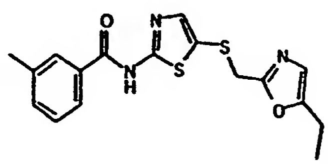
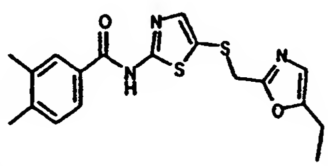
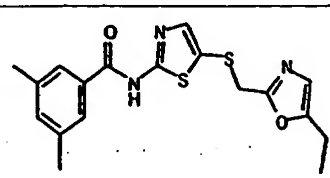
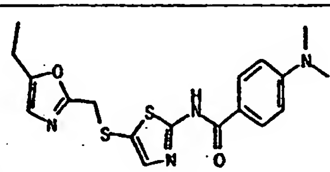
Using the procedures described herein or by modification of the procedures described herein as known to one or ordinary skill in the art, the following additional compounds have been prepared and disclosed in Table 1:

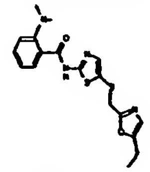
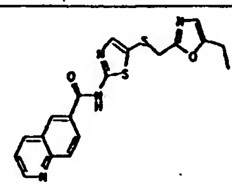
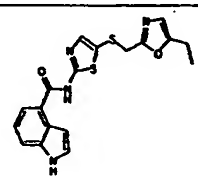
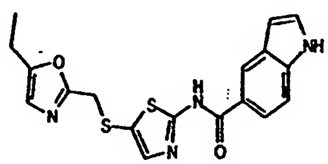
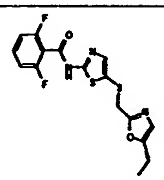
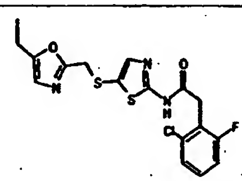
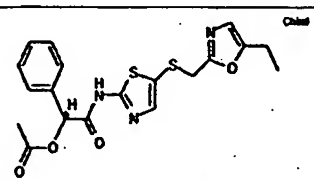
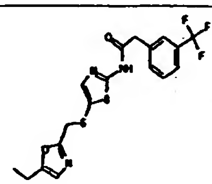
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 15 |  | C9H11N3OS2 | 242 |
| 16 |  | C12H15N3O2S2 | 298 |
| 17 |  | C13H17N3O2S2 | 312 |
| 18 |  | C11H10F3N3O2S2 | 338 |
| 19 |  | C14H19N3O2S2 | 326 |
| 20 |  | C21H17N3O2S2 | 408 |
| 21 |  | C17H24N4O2S2 | 381 |
| 22 |  | C17H17N3O2S2 | 360 |

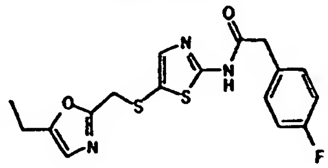
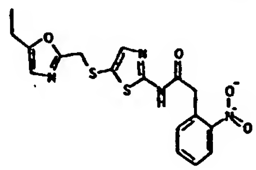
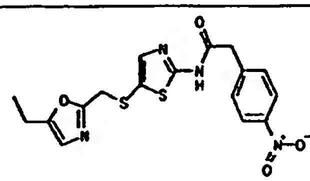
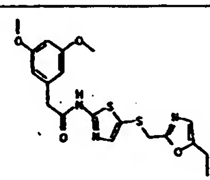
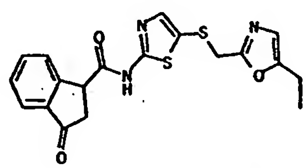
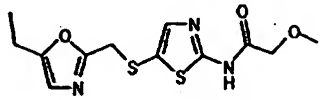
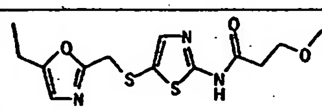
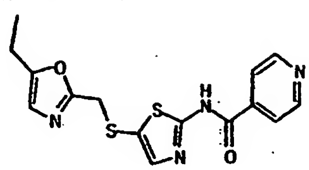
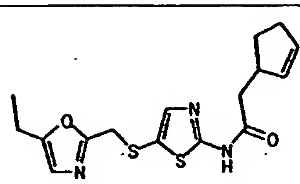
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 23 |  | C15H19N3O2S2 | 338 |
| 24 |  | C17H17N3O3S2 | 376 |
| 25 |  | C17H23N3O2S2 | 366 |
| 26 |  | C14H19N3O2S2 | 326 |
| 27 |  | C13H15N3O2S2 | 310 |
| 28 |  | C15H13N3O2S2 | 332 |
| 29 |  | C13H11N3O2S2 | 306 |
| 30 |  | C10H11N3O2S2 | 270 |
| 31 |  | C12H15N3O2S2 | 298 |

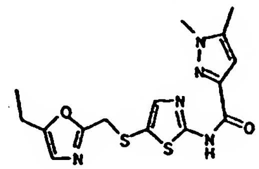
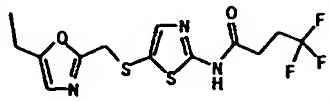
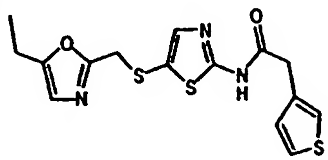
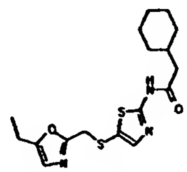
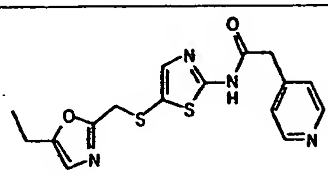
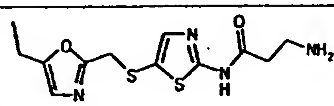
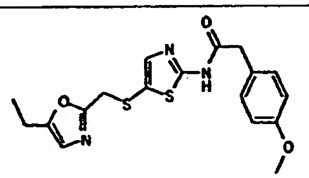
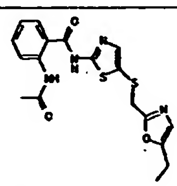
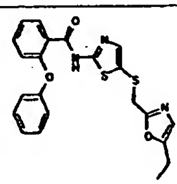
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 32 |  | C13H16BrN3O2S2 | 391 |
| 33 |  | C15H12FN3O2S2 | 350 |
| 34 |  | C13H15N3O4S2 | 342 |
| 35 |  | C15 H21 N3 O2 S2 | 340 |
| 36 |  | C19H21N3O2S2 | 388 |
| 37 |  | C18H17N3O4S2 | 404 |
| 38 |  | C15H19N3O4S2 | 370 |
| 39 |  | C14H17N3O4S2 | 356 |
| 40 |  | C16H19N3O3S2 | 366 |

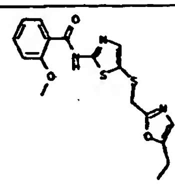
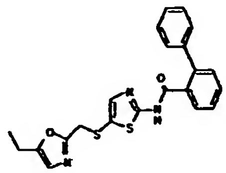
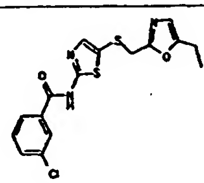
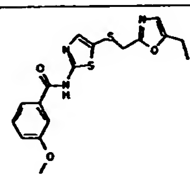
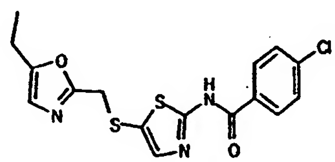
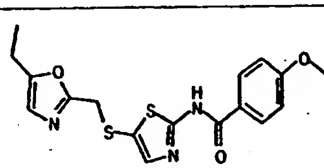
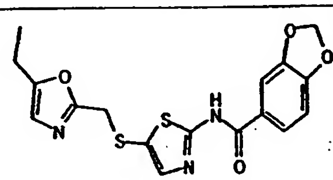
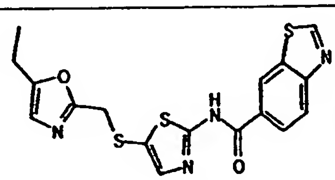
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 41 |  | C16H21N3O4S2 | 384 |
| 42 |  | C15H19N3O4S2 | 370 |
| 43 |  | C16H21N3O4S2 | 384 |
| 44 |  | C18 H17 N3 O4 S2 | 404 |
| 45 |  | C15H19N3O4S2 | 370 |
| 46 |  | C16 H14 F N3 O2 S2 | 364 |
| 47 |  | C16 H14 Cl N3 O2 S2 | 380 |
| 48 |  | C16 H13 Cl2 N3 O2 S2 | 415 |
| 49 |  | C18 H19 N3 O4 S2 | 406 |

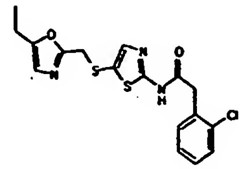
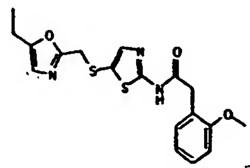
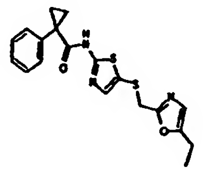
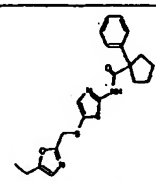
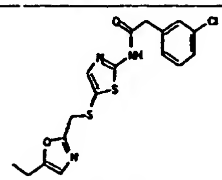
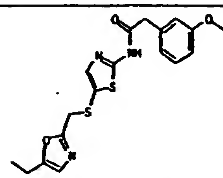
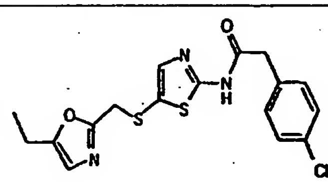
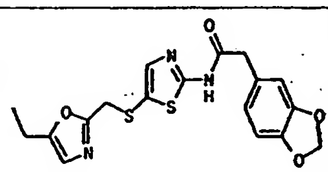
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 50 |  | C18 H19 N3 O4 S2 | 406 |
| 51 |  | C18 H19 N3 O4 S2 | 406 |
| 52 |  | C18 H19 N3 O2 S2 | 374 |
| 53 |  | C18 H20 N4 O2 S2 | 503 |
| 54 |  | C17 H17 N3 O2 S2 | 360 |
| 55 |  | C18 H19 N3 O2 S2 | 374 |
| 56 |  | C18 H19 N3 O2 S2 | 374 |
| 57 |  | C18 H20 N4 O2 S2 | 503 |

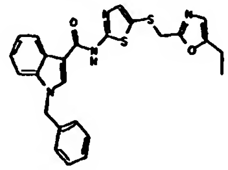
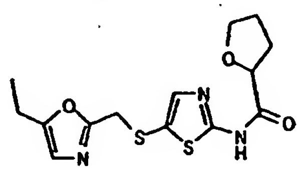
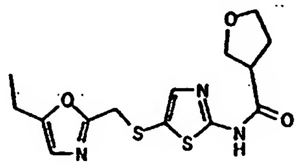
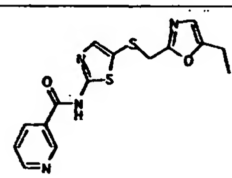
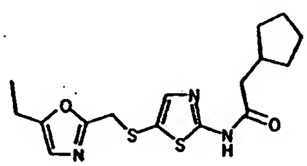
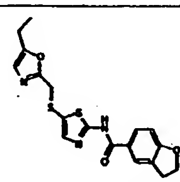
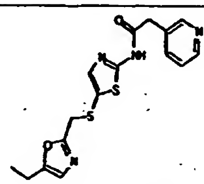
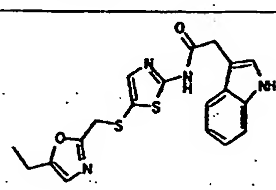
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 58 |  | C18 H20 N4 O2 S2 | 503 |
| 59 |  | C19 H16 N4 O2 S2 | 511 |
| 60 |  | C18 H16 N4 O2 S2 | 499 |
| 61 |  | C18 H16 N4 O2 S2 | 499 |
| 62 |  | C16 H13 F2 N3 O2 S2 | 382 |
| 63 |  | C17 H15 Cl F N3 O2 S2 | 412 |
| 64 |  | C19 H19 N3 O4 S2 | 418 |
| 65 |  | C18 H16 F3 N3 O2 S2 | 428 |

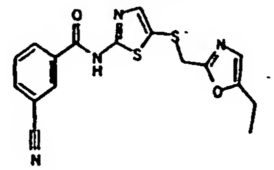
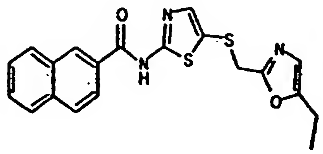
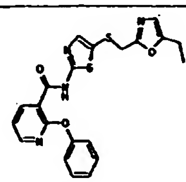
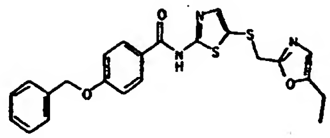
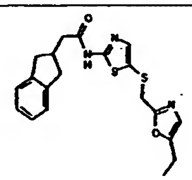
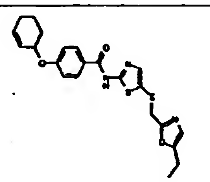
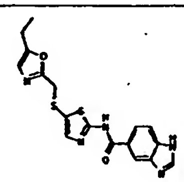
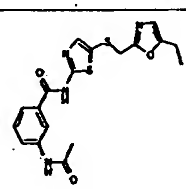
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 66 |  | C17 H16 F N3 O2 S2 | 378 |
| 67 |  | C17 H16 N4 O4 S2 | 405 |
| 68 |  | C17 H16 N4 O4 S2 | 405 |
| 69 |  | C19 H21 N3 O4 S2 | 420 |
| 70 |  | C19 H17 N3 O3 S2 | 400 |
| 71 |  | C12 H15 N3 O3 S2 | 314 |
| 72 |  | C13 H17 N3 O3 S2 | 328 |
| 73 |  | C15 H14 N4 O2 S2 | 461 |
| 74 |  | C16 H19 N3 O2 S2 | 350 |

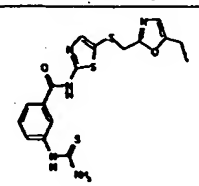
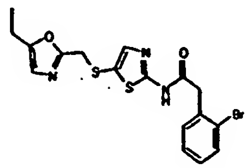
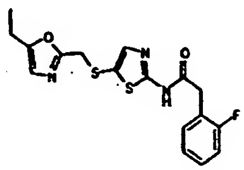
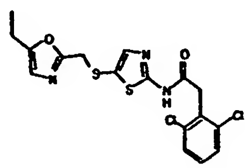
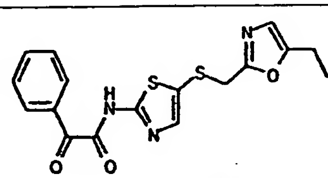
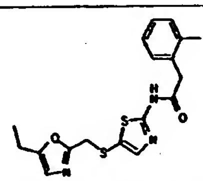
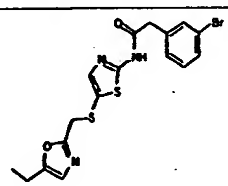
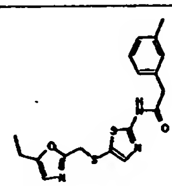
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 75 |  | C15 H17 N5 O2 S2 | 364 |
| 76 |  | C13 H14 F3 N3 O2 S2 | 366 |
| 77 |  | C15 H15 N3 O2 S3 | 366 |
| 78 |  | C17 H23 N3 O2 S2 | 366 |
| 79 |  | C16 H16 N4 O2 S2 | 475 |
| 80 |  | C12 H16 N4 O2 S2 | 427 |
| 81 |  | C18 H19 N3 O3 S2 | -390 |
| 82 |  | C18 H18 N4 O3 S2 | 403 |
| 83 |  | C22 H19 N3 O3 S2 | 438 |

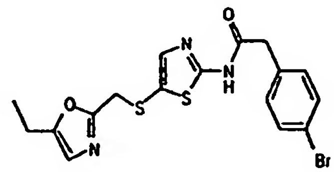
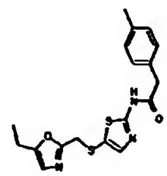
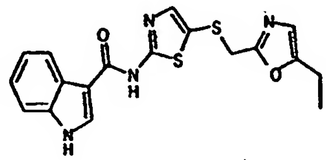
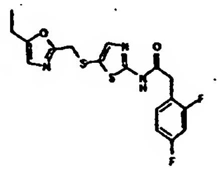
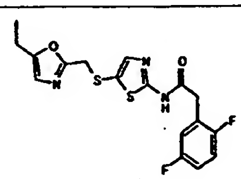
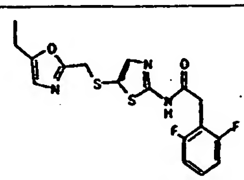
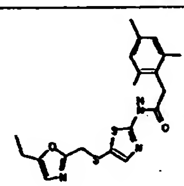
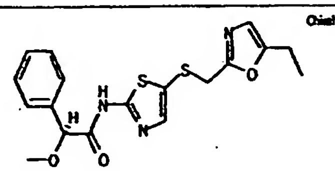
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 84 |  | C17 H17 N3 O3 S2 | 376 |
| 85 |  | C22 H19 N3 O2 S2 | 422 |
| 86 |  | C16 H14 Cl N3 O2 S2 | 380 |
| 87 |  | C17 H17 N3 O3 S2 | 376 |
| 88 |  | C16 H14 Cl N3 O2 S2 | 380 |
| 89 |  | C17 H17 N3 O3 S2 | 376 |
| 90 |  | C17 H15 N3 O4 S2 | 390 |
| 91 |  | C17 H14 N4 O2 S3 | 403 |

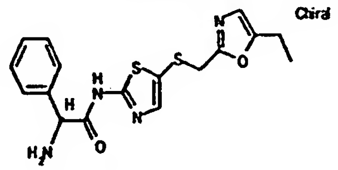
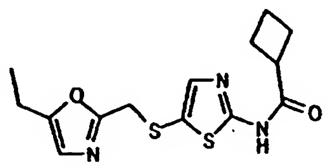
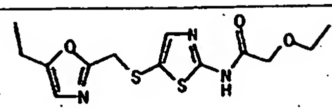
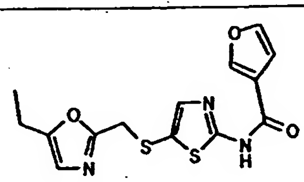
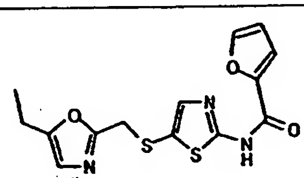
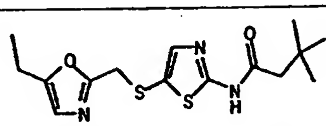
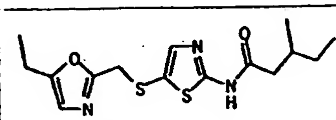
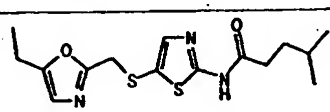
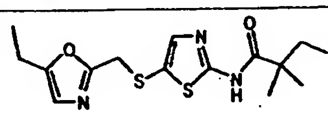
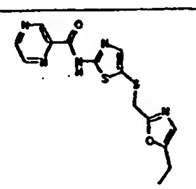
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 92 |  | C17 H16 Cl N3 O2 S2 | 394 |
| 93 |  | C18 H19 N3 O3 S2 | 390 |
| 94 |  | C19 H19 N3 O2 S2 | 386 |
| 95 |  | C21 H23 N3 O2 S2 | 414 |
| 96 |  | C17 H16 Cl N3 O2 S2 | 394 |
| 97 |  | C18 H19 N3 O3 S2 | 390 |
| 98 |  | C17 H16 Cl N3 O2 S2 | 394 |
| 99 |  | C18 H17 N3 O4 S2 | 404 |

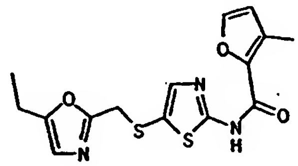
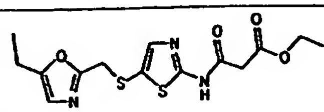
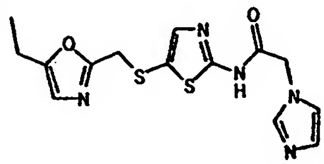
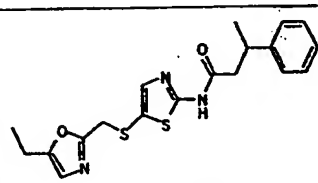
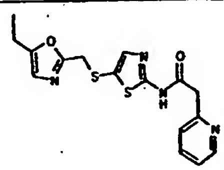
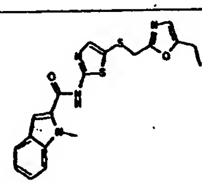
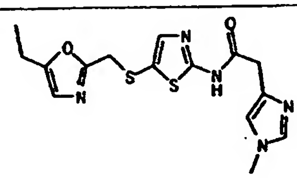
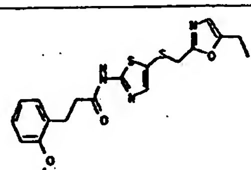
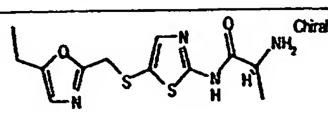
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 100 |  | C25 H22 N4 O2 S2 | 589 |
| 101 |  | C14 H17 N3 O3 S2 | 340 |
| 102 |  | C14 H17 N3 O3 S2 | 340 |
| 103 |  | C15 H14 N4 O2 S2 | 461 |
| 104 |  | C16 H21 N3 O2 S2 | 352 |
| 105 |  | C18 H17 N3 O3 S2 | 388 |
| 106 |  | C16 H16 N4 O2 S2 | 475 |
| 107 |  | C19 H18 N4 O2 S2 | 513 |

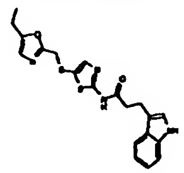
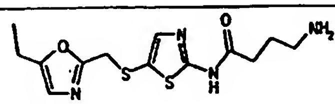
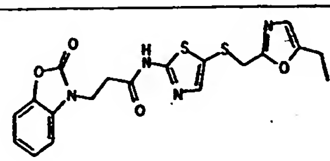
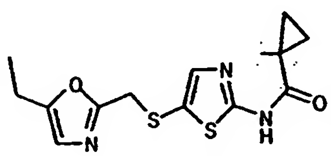
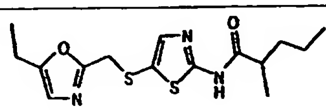
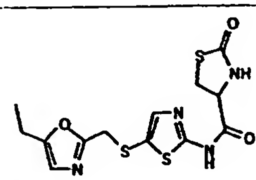
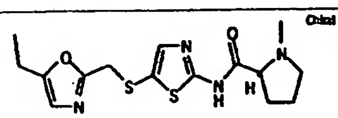
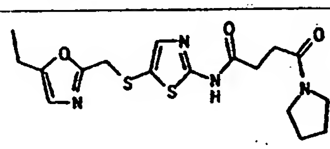
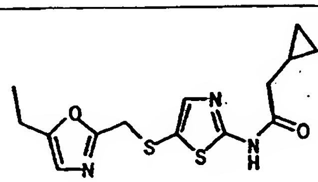
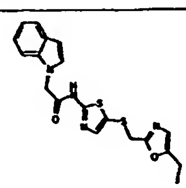
| Example | Structure | Molecular Formula | (M+H)+ |
| --- | --- | --- | --- |
| 108 |  | C17 H14 N4 O2 S2 | 371 |
| 109 |  | C20 H17 N3 O2 S2 | 396 |
| 110 |  | C21 H18 N4 O3 S2 | 553 |
| 111 |  | C23 H21 N3 O3 S2 | 452 |
| 112 |  | C20 H21 N3 O2 S2 | 400 |
| 113 |  | C22 H23 N3 O3 S2 | 442 |
| 114 |  | C17 H15 N5 O2 S2 | 500 |
| 115 |  | C18 H18 N4 O3 S2 | 403 |

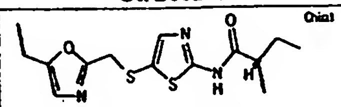
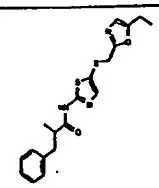
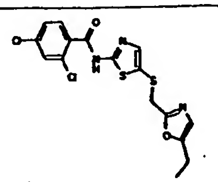
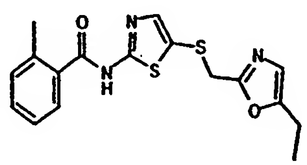
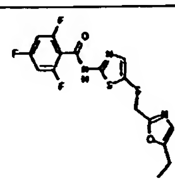
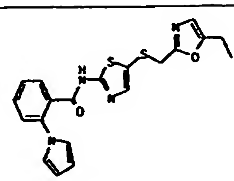
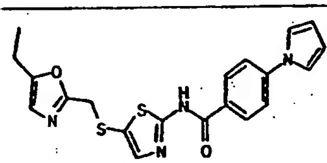
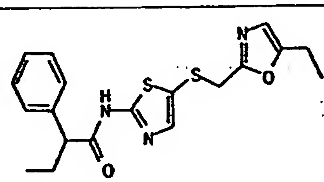
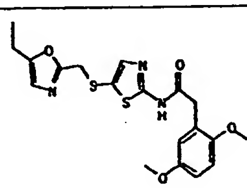
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 116 |  | C17 H17 N5 O2 S3 | 420 |
| 117 |  | C17 H16 Br N3 O2 S2 | 439 |
| 118 |  | C17 H16 F N3 O2 S2 | 378 |
| 119 |  | C17 H15 Cl2 N3 O2 S2 | 429 |
| 120 |  | C17 H15 N3 O3 S2 | 374 |
| 121 |  | C18 H19 N3 O2 S2 | 374 |
| 122 |  | C17 H16 Br N3 O2 S2 | 439 |
| 123 |  | C18 H19 N3 O2 S2 | 374 |

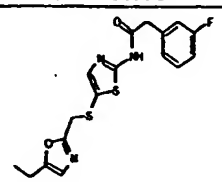
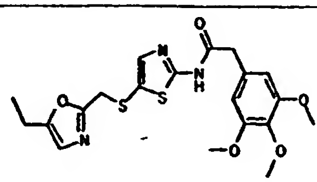
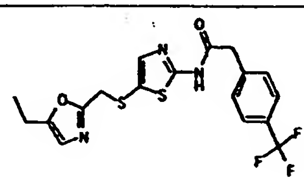
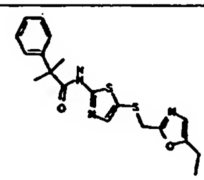
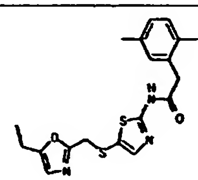
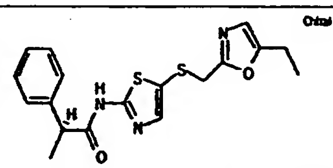
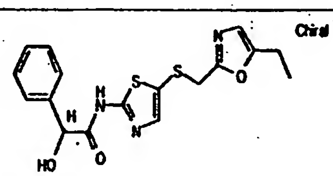
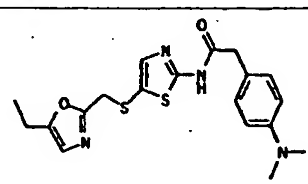
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 124 |  | C17 H16 Br N3 O2 S2 | 439 |
| 125 |  | C18 H19 N3 O2 S2 | 374 |
| 126 |  | C18 H16 N4 O2 S2 | 499 |
| 127 |  | C17 H15 F2 N3 O2 S2 | 396 |
| 128 |  | C17 H15 F2 N3 O2 S2 | 396 |
| 129 |  | C17 H15 F2 N3 O2 S2 | 396 |
| 130 |  | C20 H23 N3 O2 S2 | 402 |
| 131 |  | C18 H19 N3 O3 S2 | 390 |

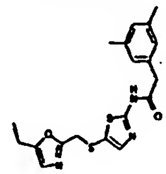
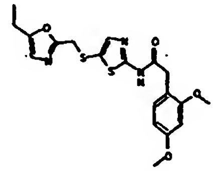
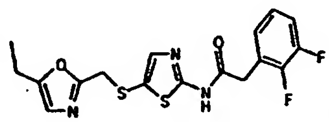
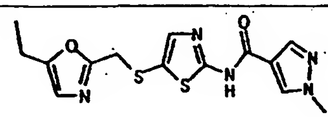
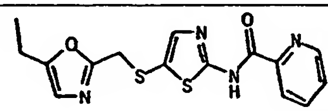
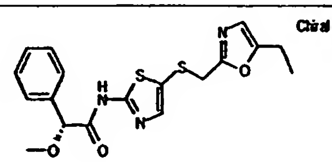
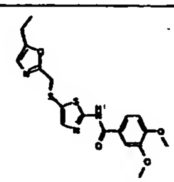
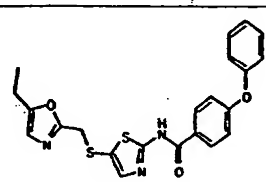
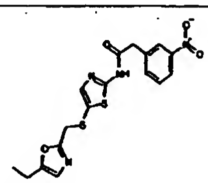
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 132 |  | C17 H18 N4 O2 S2 | 489 |
| 133 |  | C14 H17 N3 O2 S2 | 324 |
| 134 |  | C13 H17 N3 O3 S2 | 328 |
| 135 |  | C14 H13 N3 O3 S2 | 336 |
| 136 |  | C14 H13 N3 O3 S2 | 336 |
| 137 |  | C15 H21 N3 O2 S2 | 340 |
| 138 |  | C15 H21 N3 O2 S2 | 340 |
| 139 |  | C15 H21 N3 O2 S2 | 340 |
| 140 |  | C15 H21 N3 O2 S2 | 340 |
| 141 |  | C14 H13 N5 O2 S2 | 348 |

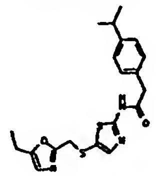
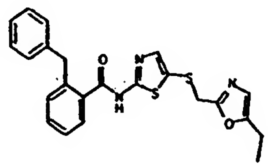
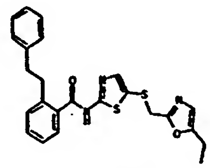
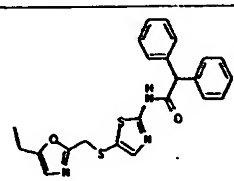
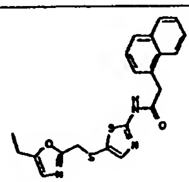
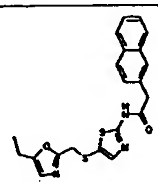
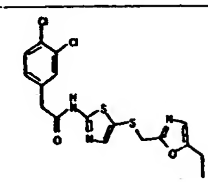
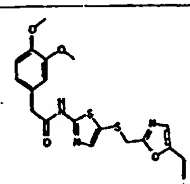
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 142 |  | C15 H15 N3 O3 S2 | 350 |
| 143 |  | C14 H17 N3 O4 S2 | 356 |
| 144 |  | C14 H15 N5 O2 S2 | 464 |
| 145 |  | C19 H21 N3 O2 S2 | 388 |
| 146 |  | C16 H16 N4 O2 S2 | 475 |
| 147 |  | C19 H18 N4 O2 S2 | 513 |
| 148 |  | C15 H17 N5 O2 S2 | 478 |
| 149 |  | C19 H21 N3 O3 S2 | 404 |
| 150 |  | C12 H16 N4 O2 S2 | 427 |

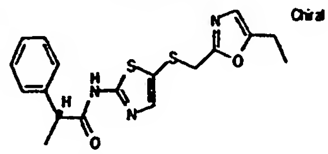
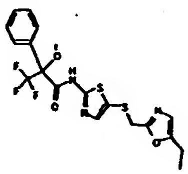
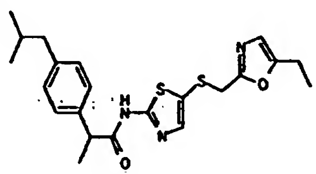
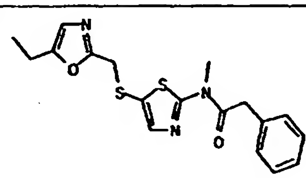
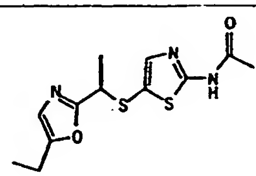
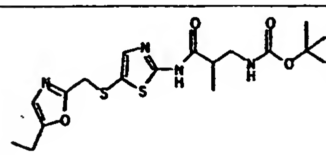
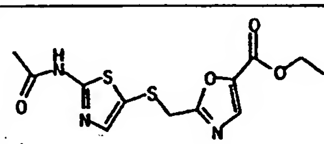
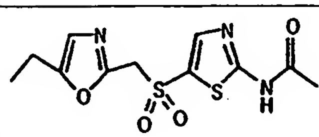
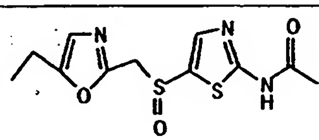
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 151 |  | C20 H20 N4 O2 S2 | 527 |
| 152 |  | C13 H18 N4 O2 S2 | 441 |
| 153 |  | C19 H18 N4 O4 S2 | 431 |
| 154 |  | C14 H17 N3 O2 S2 | 324 |
| 155 |  | C15 H21 N3 O2 S2 | 340 |
| 156 |  | C13 H14 N4 O3 S3 | 371 |
| 157 |  | C15 H20 N4 O2 S2 | 467 |
| 158 |  | C17 H22 N4 O3 S2 | 395 |
| 159 |  | C14 H17 N3 O2 S2 | 324 |
| 160 |  | C19 H18 N4 O2 S2 | 513 |

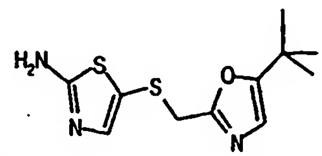
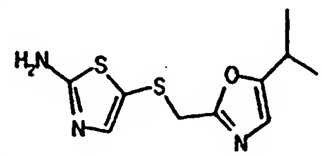
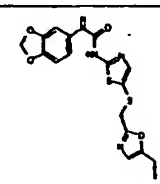
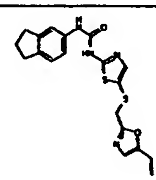
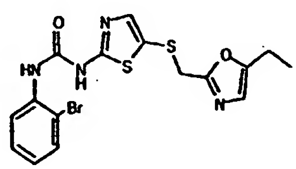
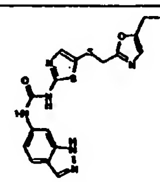
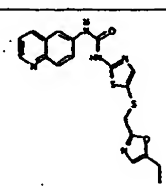
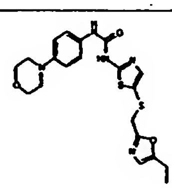
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 161 |  | C14 H19 N3 O2 S2 | 326 |
| 162 |  | C19 H21 N3 O2 S2 | 388 |
| 163 |  | C16 H13 Cl2 N3 O2 S2 | 415 |
| 164 |  | C17 H17 N3 O2 S2 | 360 |
| 165 |  | C16 H12 F3 N3 O2 S2 | 400 |
| 166 |  | C20 H18 N4 O2 S2 | 525 |
| 167 |  | C20 H18 N4 O2 S2 | 525 |
| 168 |  | C19 H21 N3 O2 S2 | 388 |
| 169 |  | C19 H21 N3 O4 S2 | 420 |

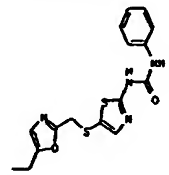
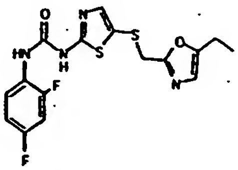
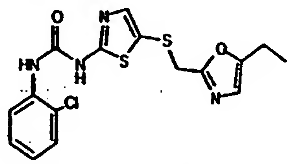
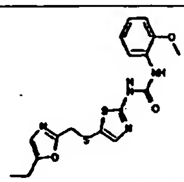
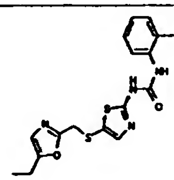
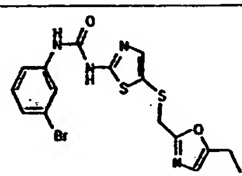
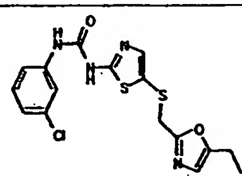
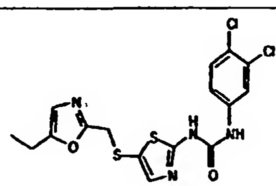
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 170 |  | C17 H16 F N3 O2 S2 | 378 |
| 171 |  | C20 H23 N3 O5 S2 | 450 |
| 172 |  | C18 H16 F3 N3 O2 S2 | 428 |
| 173 |  | C19 H21 N3 O2 S2 | 388 |
| 174 |  | C19 H21 N3 O2 S2 | 388 |
| 175 |  | C18 H19 N3 O2 S2 | 374 |
| 176 |  | C17 H17 N3 O3 S2 | 376 |
| 177 |  | C19 H22 N4 O2 S2 | 517 |

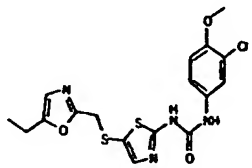
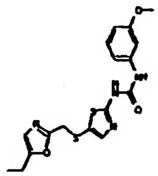
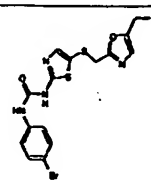
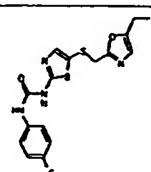
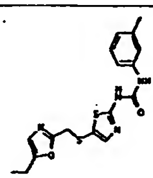
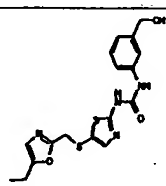
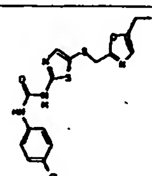
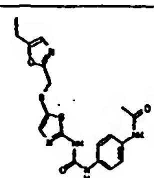
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 178 |  | C19 H21 N3 O2 S2 | 388 |
| 179 |  | C19 H21 N3 O4 S2 | 420 |
| 180 |  | C17 H15 F2 N3 O2 S2 | 396 |
| 181 |  | C14 H15 N5 O2 S2 | 350 |
| 182 |  | C15 H14 N4 O2 S2 | 461 |
| 183 |  | C18 H19 N3 O3 S2 | 390 |
| 184 |  | C18 H19 N3 O4 S2 | 406 |
| 185 |  | C22 H19 N3 O3 S2 | 438 |
| 186 |  | C17 H16 N4 O4 S2 | 405 |

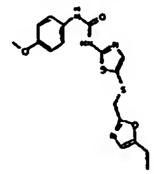
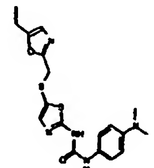
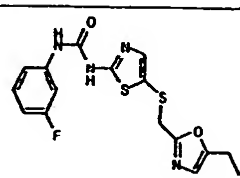
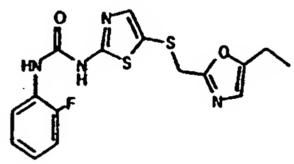
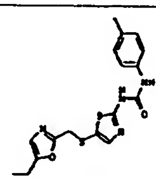
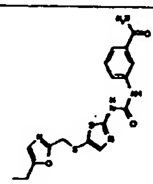
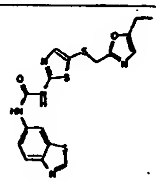
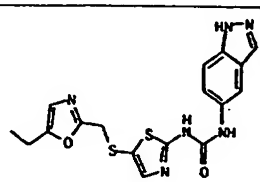
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 187 |  | C20 H23 N3 O2 S2 | 402 |
| 188 |  | C23 H21 N3 O2 S2 | 436 |
| 189 |  | C24 H23 N3 O2 S2 | 450 |
| 190 |  | C23 H21 N3 O2 S2 | 436 |
| 191 |  | C21 H19 N3 O2 S2 | 410 |
| 192 |  | C21 H19 N3 O2 S2 | 410 |
| 193 |  | C17 H15 Cl2 N3 O2 S2 | 429 |
| 194 |  | C19 H21 N3 O4 S2 | 420 |

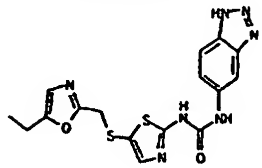
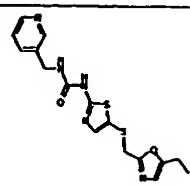
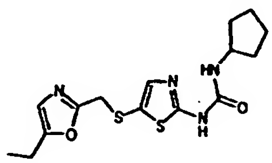
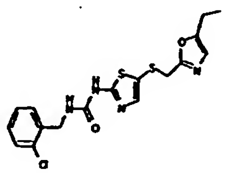
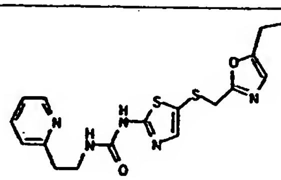
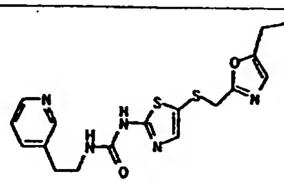
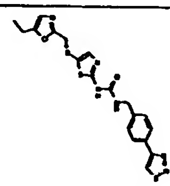
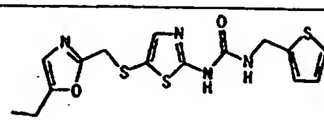
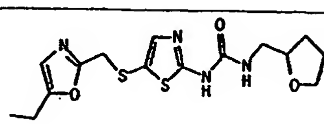
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 195 |  | C18 H19 N3 O2 S2 | 374 |
| 196 |  | C19 H18 F3 N3 O3 S2 | 458 |
| 197 |  | C22 H27 N3 O2 S2 | 430 |
| 198 |  | C18 H19 N3 O2 S2 | 374 |
| 199 |  | C12 H15 N3 O2 S2 | 298 |
| 200 |  | C18 H26 N4 O4 S2 | 427 |
| 201 |  | C12 H13 N3 O4 S2 | 328 |
| 202 |  | C11 H13 N3 O4 S2 | 316 |
| 203 |  | C11 H13 N3 O3 S2 | 300 |

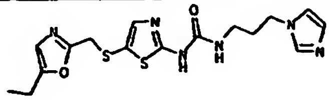
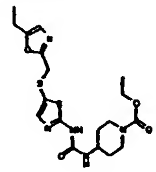
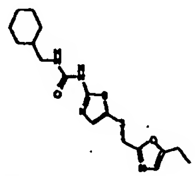
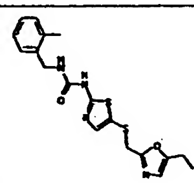
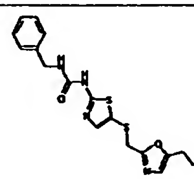
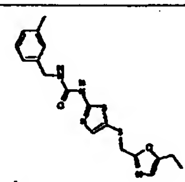
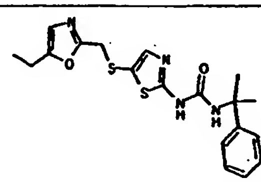
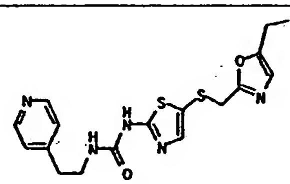
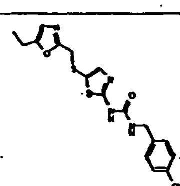
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 204 |  | C11 H15 N3 O S2 | 270 |
| 205 |  | C10 H13 N3 O S2 | 256 |
| 206 |  | C17 H16 N4 O4 S2 | 405 |
| 207 |  | C19 H20 N4 O2 S2 | 401 |
| 208 |  | C16 H15 Br N4 O2 S2 | 440 |
| 209 |  | C17 H16 N6 O2 S2 | 515 |
| 210 |  | C19 H17 N5 O2 S2 | 526 |
| 211 |  | C20 H23 N5 O3 S2 | 560 |

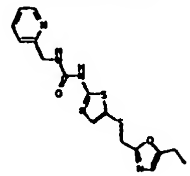
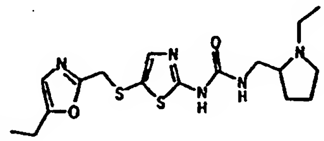
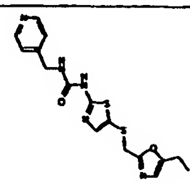
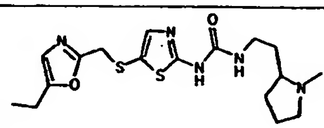
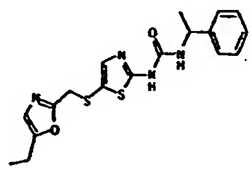
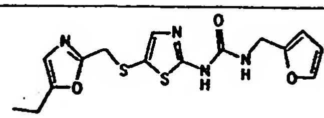
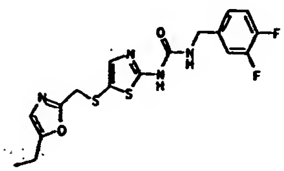
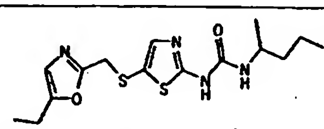
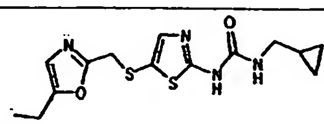
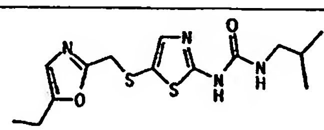
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 212 |  | C16 H16 N4 O2 S2 | 361 |
| 213 |  | C16 H14 F2 N4 O2 S2 | 397 |
| 214 |  | C16 H15 Cl N4 O2 S2 | 395 |
| 215 |  | C17 H18 N4 O3 S2 | 391 |
| 216 |  | C17 H18 N4 O2 S2 | 375 |
| 217 |  | C16 H15 Br N4 O2 S2 | 440 |
| 218 |  | C16 H15 Cl N4 O2 S2 | 395 |
| 219 |  | C16 H14 Cl2 N4 O2 S2 | 430 |

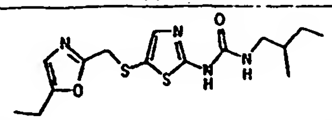
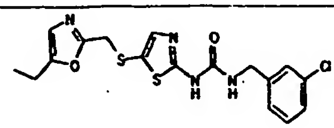
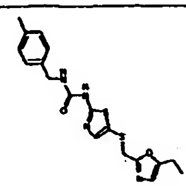
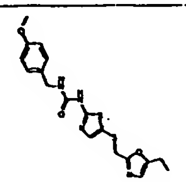
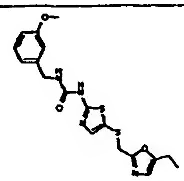
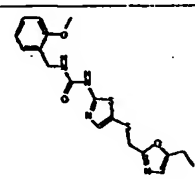
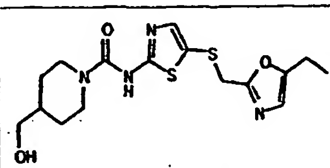
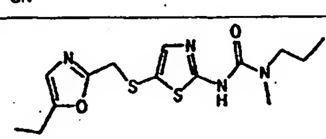
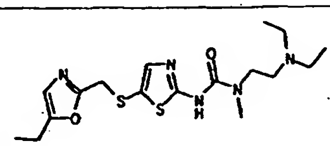
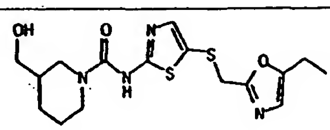
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 220 |  | C17 H17 Cl N4 O3 S2 | 425 |
| 221 |  | C17 H18 N4 O3 S2 | 391 |
| 222 |  | C16 H15 Br N4 O2 S2 | 440 |
| 223 |  | C16 H15 F N4 O2 S2 | 379 |
| 224 |  | C17 H18 N4 O2 S2 | 375 |
| 225 |  | C17 H18 N4 O3 S2 | 391 |
| 226 |  | C16 H15 Cl N4 O2 S2 | 395 |
| 227 |  | C18 H19 N5 O3 S2 | 418 |

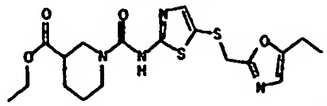
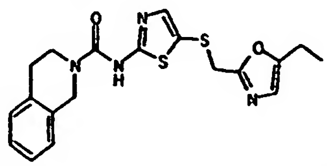
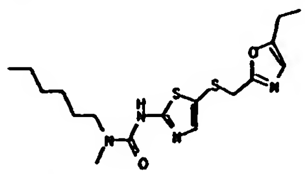
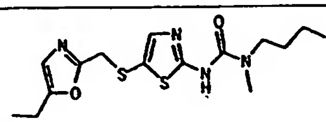
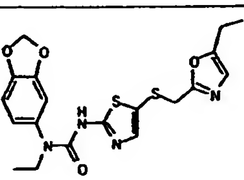
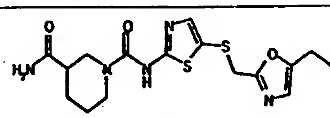
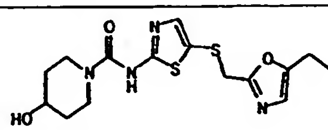
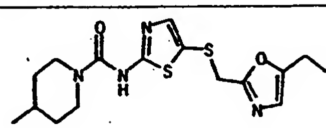
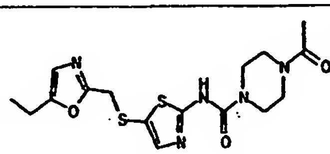
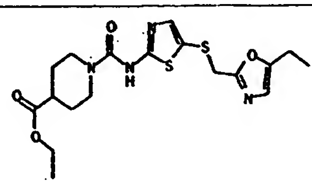
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 228 |  | C17 H18 N4 O3 S2 | 391 |
| 229 |  | C18 H21 N5 O2 S2 | 518 |
| 230 |  | C16 H15 F N4 O2 S2 | 379 |
| 231 |  | C16 H15 F N4 O2 S2 | 379 |
| 232 |  | C17 H18 N4 O2 S2 | 375 |
| 233 |  | C17 H17 N5 O3 S2 | 404 |
| 234 |  | C17 H15 N5 O2 S3 | 418 |
| 235 |  | C17 H16 N6 O2 S2 | 401 |

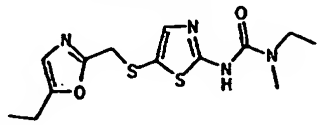
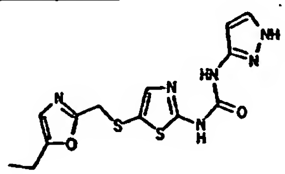
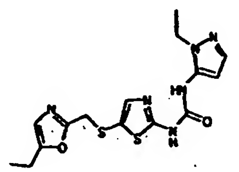
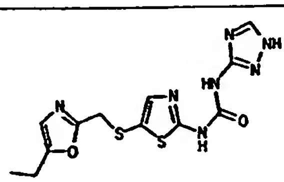
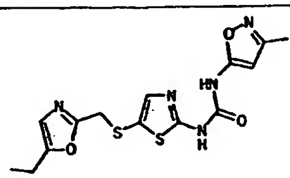
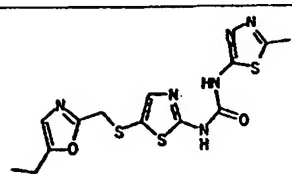
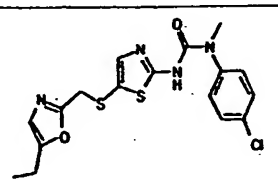
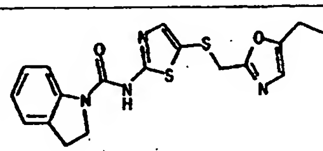
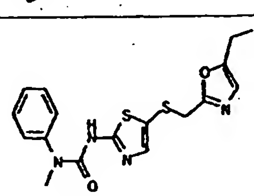
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 236 |  | C16 H15 N7 O2 S2 | 402 |
| 237 |  | C16 H17 N5 O2 S2 | 490 |
| 238 |  | C15 H20 N4 O2 S2 | 353 |
| 239 |  | C17 H17 Cl N4 O2 S2 | 409 |
| 240 |  | C17 H19 N5 O2 S2 | 504 |
| 241 |  | C17 H19 N5 O2 S2 | 504 |
| 242 |  | C19 H18 N6 O2 S3 | 459 |
| 243 |  | C15 H16 N4 O2 S3 | 381 |
| 244 |  | C15 H20 N4 O3 S2 | 369 |

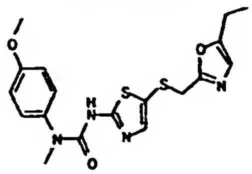
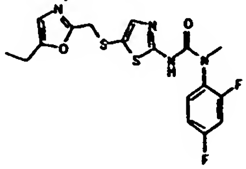
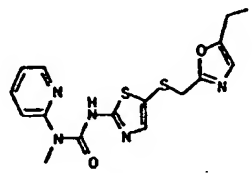
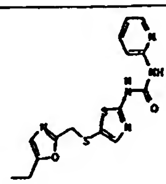
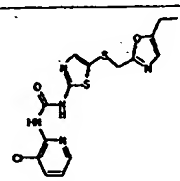
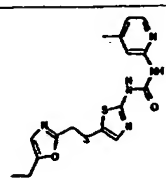
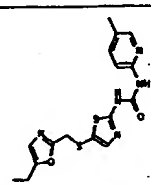
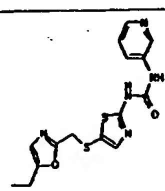
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 245 |  | C16 H20 N6 O2 S2 | 507 |
| 246 |  | C18 H25 N5 O4 S2 | 440 |
| 247 |  | C17 H24 N4 O2 S2 | 381 |
| 248 |  | C18 H20 N4 O2 S2 | 389 |
| 249 |  | C17 H18 N4 O2 S2 | 375 |
| 250 |  | C18 H20 N4 O2 S2 | 389 |
| 251 |  | C19 H22 N4 O2 S2 | 403 |
| 252 |  | C17 H19 N5 O2 S2 | 504 |
| 253 |  | C17 H17 Cl N4 O2 S2 | 409 |

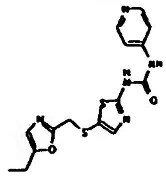
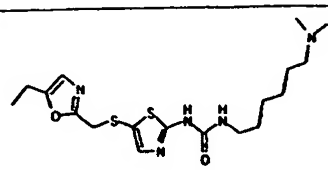
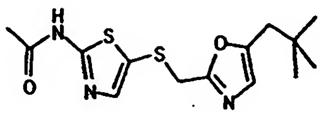
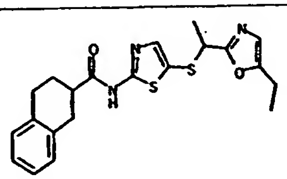
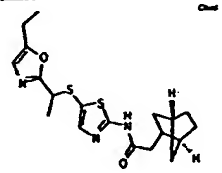
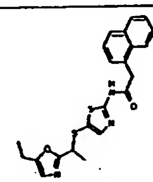
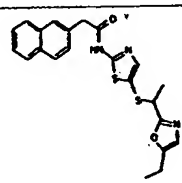
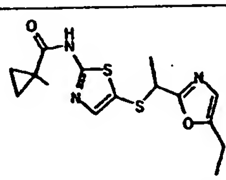
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 254 |  | C16 H17 N5 O2 S2 | 490 |
| 255 |  | C17 H25 N5 O2 S2 | 510 |
| 256 |  | C16 H17 N5 O2 S2 | 490 |
| 257 |  | C17 H25 N5 O2 S2 | 510 |
| 258 |  | C18 H20 N4 O2 S2 | 389 |
| 259 |  | C15 H16 N4 O3 S2 | 365 |
| 260 |  | C17 H16 F2 N4 O2 S2 | 411 |
| 261 |  | C15 H22 N4 O2 S2 | 355 |
| 262 |  | C14 H18 N4 O2 S2 | 339 |
| 263 |  | C14 H20 N4 O2 S2 | 341 |

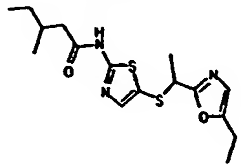
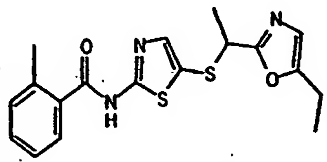
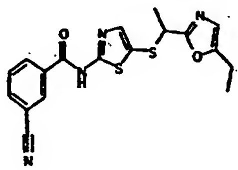
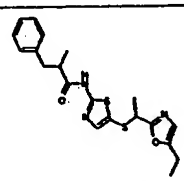
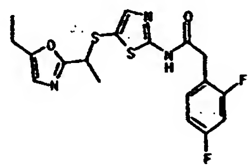
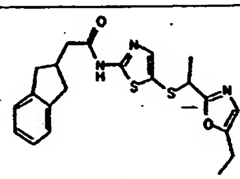
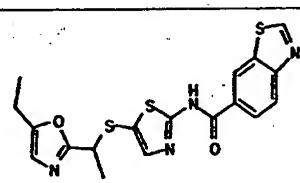
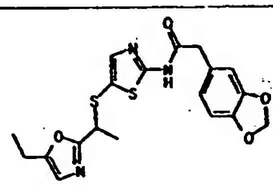
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 264 |  | C15 H22 N4 O2 S2 | 355 |
| 265 |  | C17 H17 Cl N4 O2 S2 | 409 |
| 266 |  | C18 H20 N4 O2 S2 | 389 |
| 267 |  | C18 H20 N4 O3 S2 | 405 |
| 268 |  | C18 H20 N4 O3 S2 | 405 |
| 269 |  | C18 H20 N4 O3 S2 | 405 |
| 270 |  | C16 H22 N4 O3 S2 | 341 |
| 271 |  | C14 H20 N4 O2 S2 | 512 |
| 272 |  | C17 H27 N5 O2 S2 | 353 |
| 273 |  | C16 H22 N4 O3 S2 | 425 |

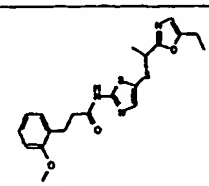
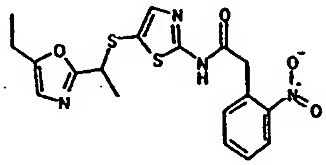
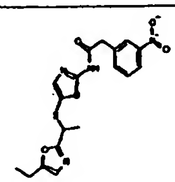
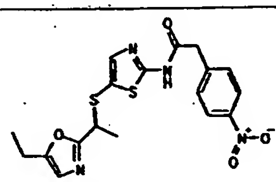
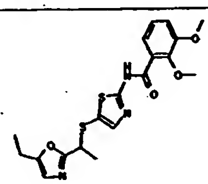
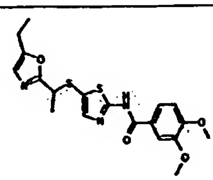
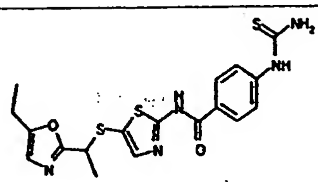
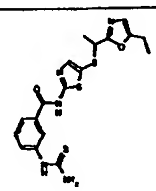
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 274 |  | C18 H24 N4 O4 S2 | 401 |
| 275 |  | C19 H20 N4 O2 S2 | 383 |
| 276 |  | C17 H26 N4 O2 S2 | 355 |
| 277 |  | C15 H22 N4 O2 S2 | 433 |
| 278 |  | C19 H20 N4 O4 S2 | 512 |
| 279 |  | C16 H21 N5 O3 S2 | 353 |
| 280 |  | C15 H20 N4 O3 S2 | 367 |
| 281 |  | C16 H22 N4 O2 S2 | 389 |
| 282 |  | C16 H21 N5 O3 S2 | 425 |
| 283 |  | C18 H24 N4 O4 S2 | 369 |

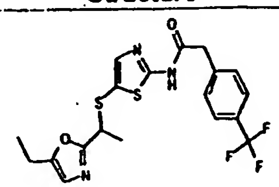
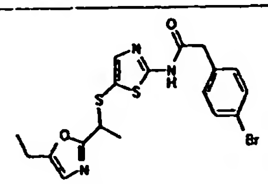
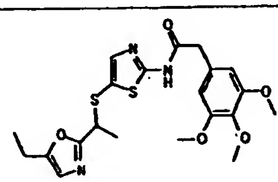
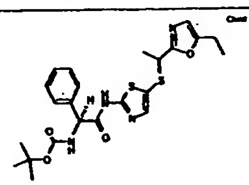
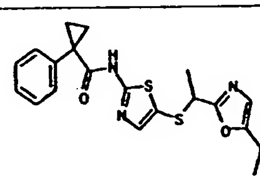
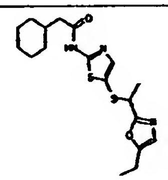
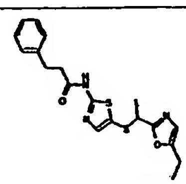
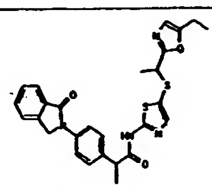
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 284 |  | C13 H18 N4 O2 S2 | 465 |
| 285 |  | C13 H14 N6 O2 S2 | 493 |
| 286 |  | C15 H18 N6 O2 S2 | 466 |
| 287 |  | C12 H13 N7 O2 S2 | 366 |
| 288 |  | C14 H15 N5 O3 S2 | 366 |
| 289 |  | C13 H14 N6 O2 S3 | 409 |
| 290 |  | C17 H17 Cl N4 O2 S2 | 387 |
| 291 |  | C18 H18 N4 O2 S2 | 375 |
| 292 |  | C17 H18 N4 O2 S2 | 405 |

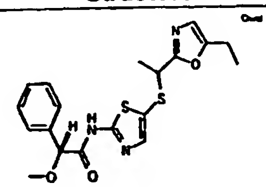
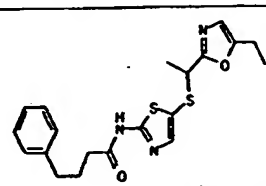
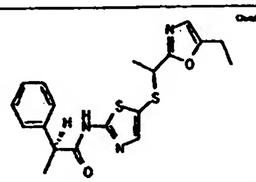
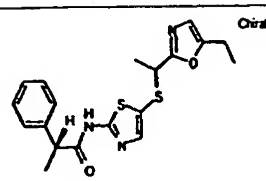
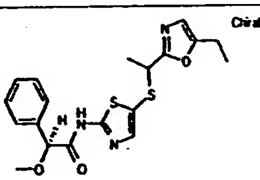
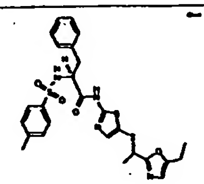
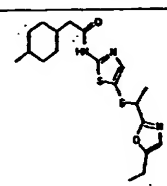
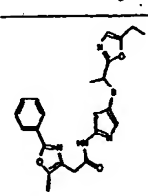
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 293 |  | C18 H20 N4 O3 S2 | 389 |
| 294 |  | C17 H16 F2 N4 O2 S2 | 490 |
| 295 |  | C16 H17 N5 O2 S2 | 476 |
| 296 |  | C15 H15 N5 O2 S2 | 510 |
| 297 |  | C15 H14 Cl N5 O2 S2 | 490 |
| 298 |  | C16 H17 N5 O2 S2 | 490 |
| 299 |  | C16 H17 N5 O2 S2 | 476 |
| 300 |  | C15 H15 N5 O2 S2 | 526 |

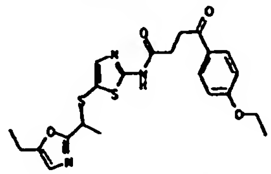
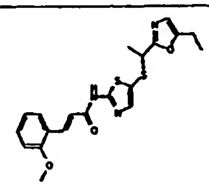
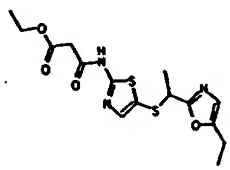
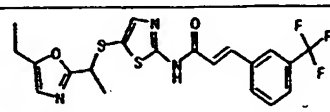
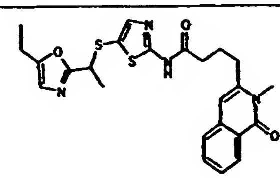
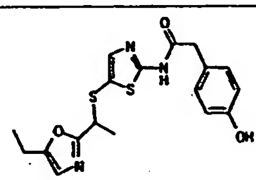
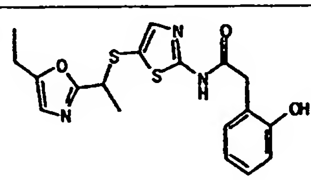
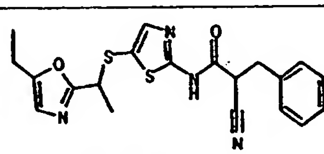
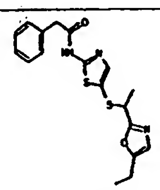
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 301 |  | C15 H15 N5 O2 S2 | 540 |
| 302 |  | C18 H29 N5 O2 S2 | 526 |
| 303 |  | C14 H19 N3 O2 S2 | 326 |
| 304 |  | C21 H23 N3 O2 S2 | 414 |
| 305 |  | C19 H25 N3 O2 S2 | 392 |
| 306 |  | C22 H21 N3 O2 S2 | 424 |
| 307 |  | C22 H21 N3 O2 S2 | 424 |
| 308 |  | C15 H19 N3 O2 S2 | 338 |

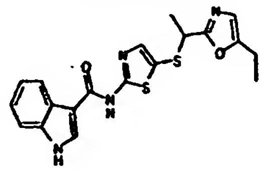
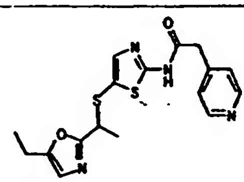
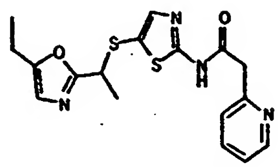
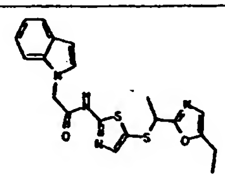
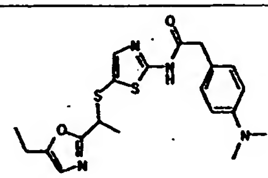
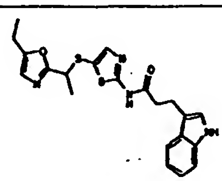
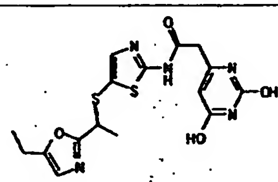
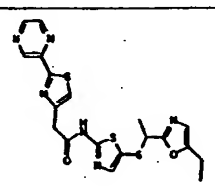
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 309 |  | C16 H23 N3 O2 S2 | 354 |
| 310 |  | C18 H19 N3 O2 S2 | 374 |
| 311 |  | C18 H16 N4 O2 S2 | 385 |
| 312 |  | C20 H23 N3 O2 S2 | 402 |
| 313 |  | C18 H17 F2 N3 O2 S2 | 410 |
| 314 |  | C21 H23 N3 O2 S2 | 414 |
| 315 |  | C18 H16 N4 O2 S3 | 417 |
| 316 |  | C19 H19 N3 O4 S2 | 418 |

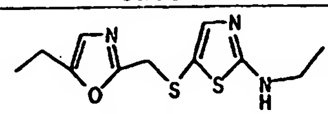
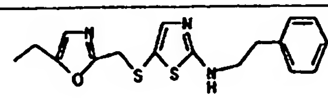
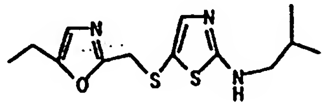
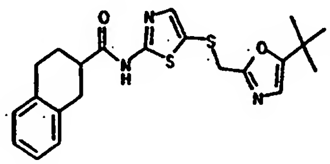
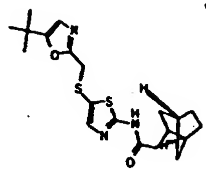
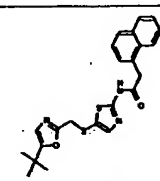
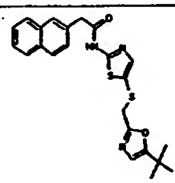
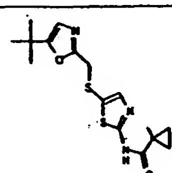
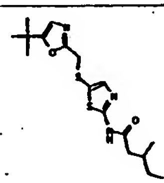
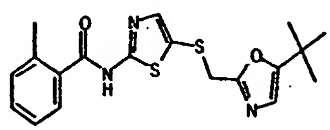
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 317 |  | C20 H23 N3 O3 S2 | 418 |
| 318 |  | C18 H18 N4 O4 S2 | 419 |
| 319 |  | C18 H18 N4 O4 S2 | 419 |
| 320 |  | C18 H18 N4 O4 S2 | 419 |
| 321 |  | C19 H21 N3 O4 S2 | 420 |
| 322 |  | C19 H21 N3 O4 S2 | 420 |
| 323 |  | C18 H19 N5 O2 S3 | 434 |
| 324 |  | C18 H19 N5 O2 S3 | 434 |

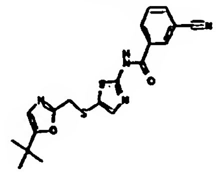
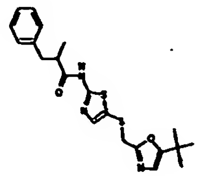
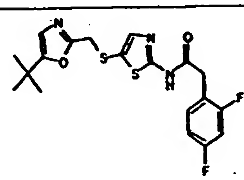
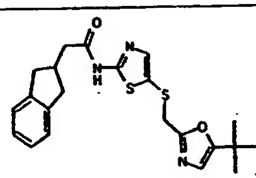
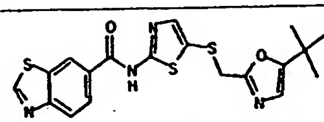
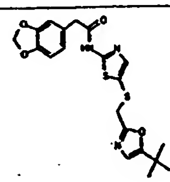
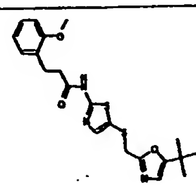
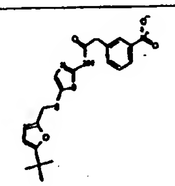
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 325 |  | C19 H18 F3 N3 O2 S2 | 442 |
| 326 |  | C18 H18 Br N3 O2 S2 | 453 |
| 327 |  | C21 H25 N3 O5 S2 | 464 |
| 328 |  | C23 H28 N4 O4 S2 | 489 |
| 329 |  | C20 H21 N3 O2 S2 | 400 |
| 330 |  | C18 H25 N3 O2 S2 | 380 |
| 331 |  | C19 H21 N3 O2 S2 | 388 |
| 332 |  | C27 H26 N4 O3 S2 | 519 |

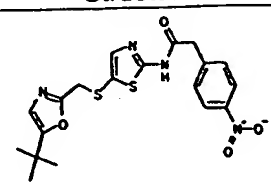
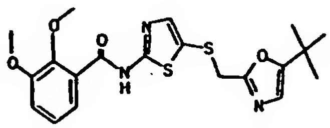
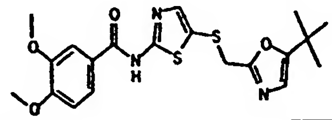
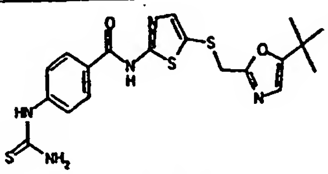
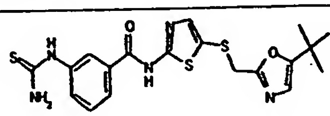
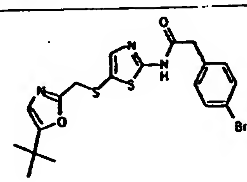
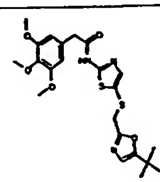
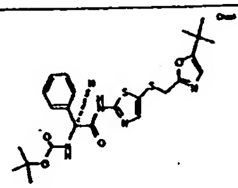
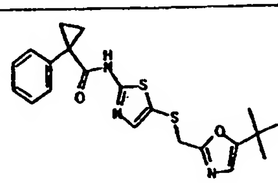
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 333 |  | C19 H21 N3 O3 S2 | 404 |
| 334 |  | C20 H23 N3 O2 S2 | 402 |
| 335 |  | C19 H21 N3 O2 S2 | 388 |
| 336 |  | C19 H21 N3 O2 S2 | 388 |
| 337 |  | C19 H21 N3 O3 S2 | 404 |
| 338 |  | C26 H28 N4 O4 S3 | 557 |
| 339 |  | C19 H27 N3 O2 S2 | 394 |
| 340 |  | C22 H22 N4 O3 S2 | 455 |

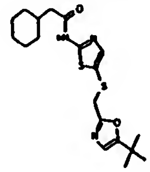
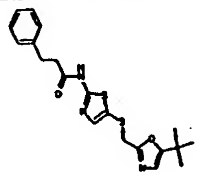
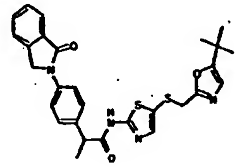
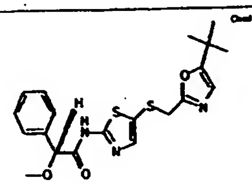
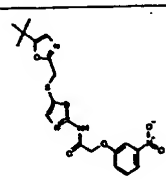
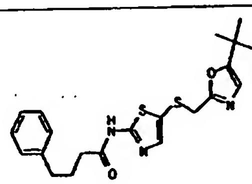
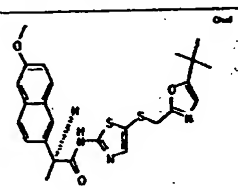
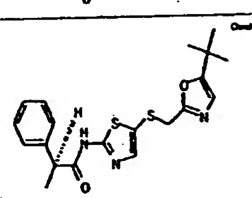
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 341 |  | C22 H25 N3 O4 S2 | 460 |
| 342 |  | C20 H21 N3 O3 S2 | 416 |
| 343 |  | C15 H19 N3 O4 S2 | 370 |
| 344 |  | C20 H18 F3 N3 O2 S2 | 454 |
| 345 |  | C24 H26 N4 O3 S2 | 483 |
| 346 |  | C18 H19 N3 O3 S2 | 390 |
| 347 |  | C18 H19 N3 O3 S2 | 390 |
| 348 |  | C20 H20 N4 O2 S2 | 413 |
| 349 |  | C18 H19 N3 O2 S2 | 374 |

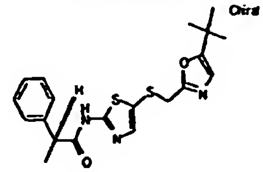
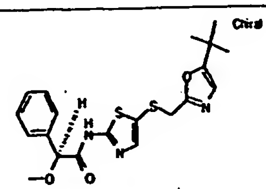
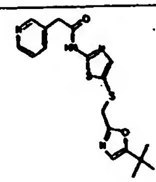
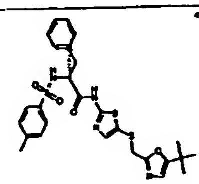
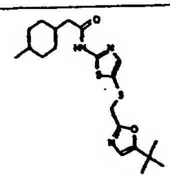
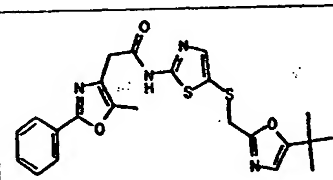
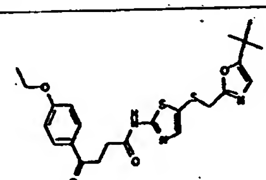
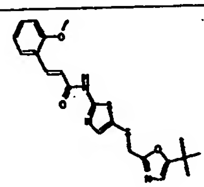
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 350 |  | C19 H18 N4 O2 S2 | 399 |
| 351 |  | C17 H18 N4 O2 S2 | 489 |
| 352 |  | C17 H18 N4 O2 S2 | 489 |
| 353 |  | C20 H20 N4 O2 S2 | 413 |
| 354 |  | C20 H24 N4 O2 S2 | 531 |
| 355 |  | C21 H22 N4 O2 S2 | 427 |
| 356 |  | C16 H17 N5 O4 S2 | 408 |
| 357 |  | C19 H18 N6 O2 S3 | 687 |

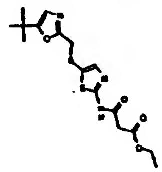
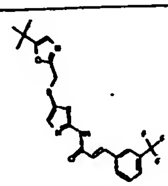
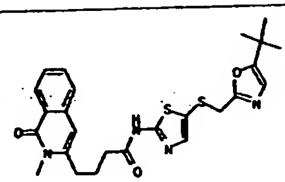
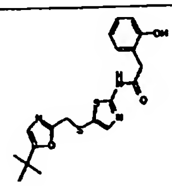
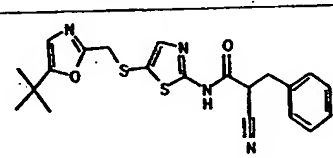
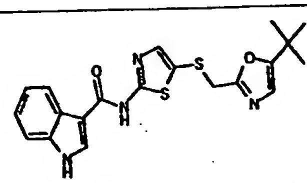
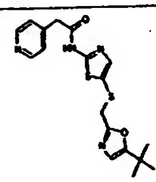
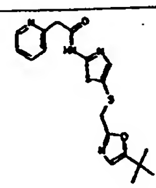
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 358 |  | C11 H15 N3 O S2 | 270 |
| 359 |  | C17 H19 N3 O S2 | 346 |
| 360 |  | C13 H19 N3 O S2 | 298 |
| 361 |  | C22 H25 N3 O2 S2 | 428 |
| 362 |  | C20 H27 N3 O2 S2 | 406 |
| 363 |  | C23 H23 N3 O2 S2 | 438 |
| 364 |  | C23 H23 N3 O2 S2 | 438 |
| 365 |  | C16 H21 N3 O2 S2 | 352 |
| 366 |  | C17 H25 N3 O2 S2 | 368 |
| 367 |  | C19 H21 N3 O2 S2 | 388 |

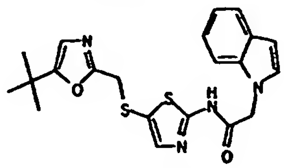
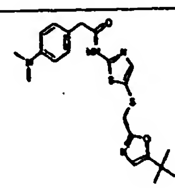
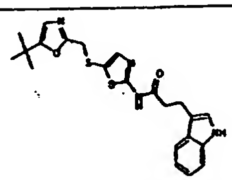
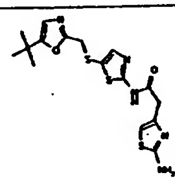
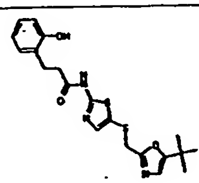
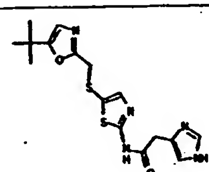
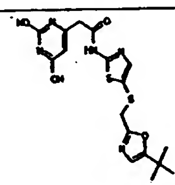
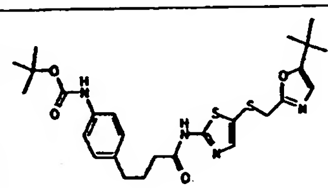
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 368 |  | C19 H18 N4 O2 S2 | 399 |
| 369 |  | C21 H25 N3 O2 S2 | 416 |
| 370 |  | C19 H19 F2 N3 O2 S2 | 424 |
| 371 |  | C22 H25 N3 O2 S2 | 428 |
| 372 |  | C19 H18 N4 O2 S3 | 431 |
| 373 |  | C20 H21 N3 O4 S2 | 432 |
| 374 |  | C21 H25 N3 O3 S2 | 432 |
| 375 |  | C19 H20 N4 O4 S2 | 433 |

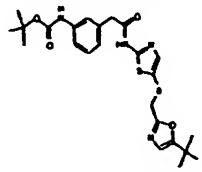
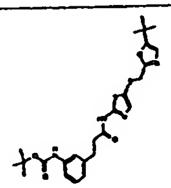
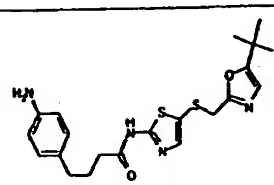
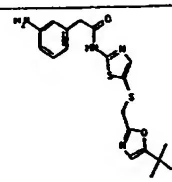
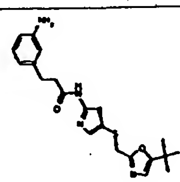
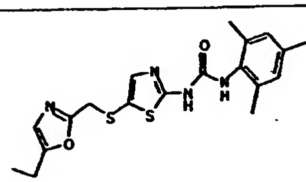
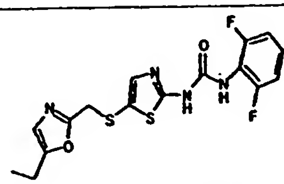
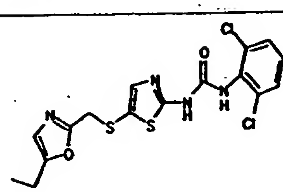
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 376 |  | C19 H20 N4 O4 S2 | 433 |
| 377 |  | C20 H23 N3 O4 S2 | 434 |
| 378 |  | C20 H23 N3 O4 S2 | 434 |
| 379 |  | C19 H21 N5 O2 S3 | 448 |
| 380 |  | C19 H21 N5 O2 S3 | 448 |
| 381 |  | C19 H20 Br N3 O2 S2 | 467 |
| 382 |  | C22 H27 N3 O5 S2 | 478 |
| 383 |  | C24 H30 N4 O4 S2 | 503 |
| 384 |  | C21 H23 N3 O2 S2 | 414 |

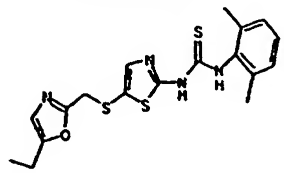
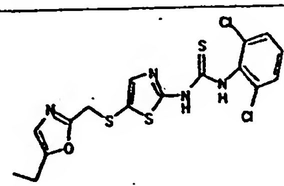
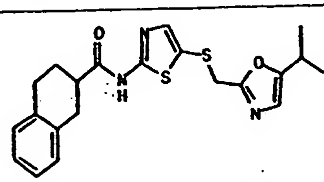
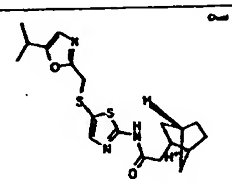
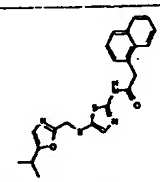
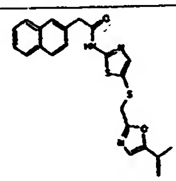
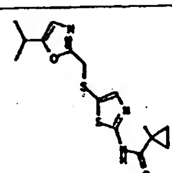
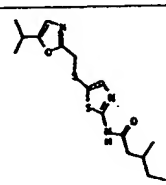
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 385 |  | C19 H27 N3 O2 S2 | 394 |
| 386 |  | C20 H23 N3 O2 S2 | 402 |
| 387 |  | C28 H28 N4 O3 S2 | 533 |
| 388 |  | C20 H23 N3 O3 S2 | 418 |
| 389 |  | C19 H20 N4 O5 S2 | 449 |
| 390 |  | C21 H25 N3 O2 S2 | 416 |
| 391 |  | C25 H27 N3 O3 S2 | 482 |
| 392 |  | C20 H23 N3 O2 S2 | 402 |

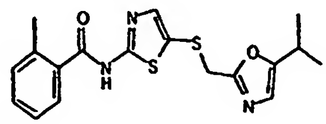
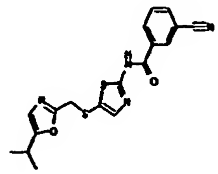
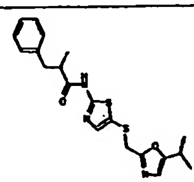
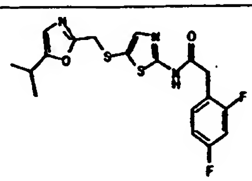
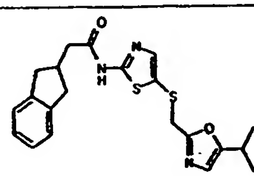
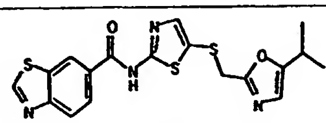
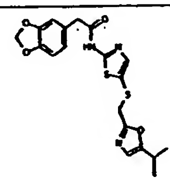
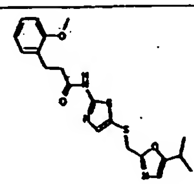
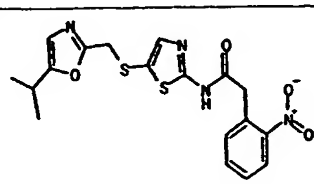
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 393 |  | C20 H23 N3 O2 S2 | 402 |
| 394 |  | C20 H23 N3 O3 S2 | 418 |
| 395 |  | C18 H20 N4 O2 S2 | 503 |
| 396 |  | C27 H30 N4 O4 S3 | 571 |
| 397 |  | C20 H29 N3 O2 S2 | 408 |
| 398 |  | C23 H24 N4 O3 S2 | 469 |
| 399 |  | C23 H27 N3 O4 S2 | 474 |
| 400 |  | C21 H23 N3 O3 S2 | 430 |

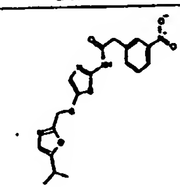
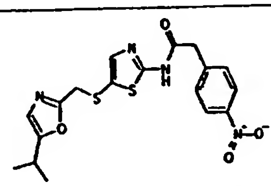
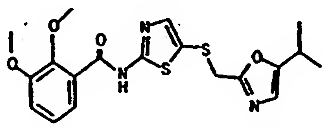
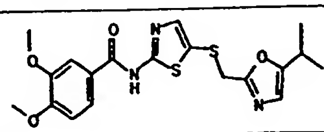
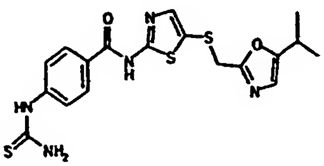
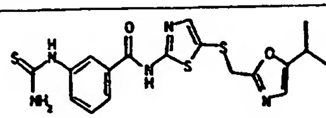
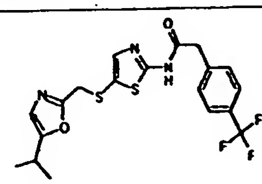
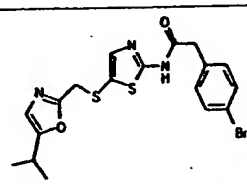
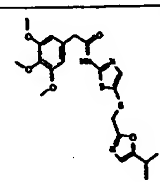
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 401 |  | C16 H21 N3 O4 S2 | 384 |
| 402 |  | C21 H20 F3 N3 O2 S2 | 468 |
| 403 |  | C25 H28 N4 O3 S2 | 497 |
| 404 |  | C19 H21 N3 O3 S2 | 404 |
| 405 |  | C21 H22 N4 O2 S2 | 427 |
| 406 |  | C20 H20 N4 O2 S2 | 413 |
| 407 |  | C18 H20 N4 O2 S2 | 503 |
| 408 |  | C18 H20 N4 O2 S2 | 503 |

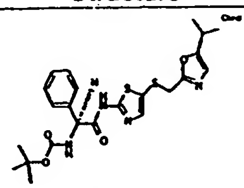
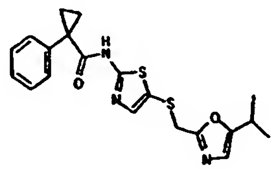
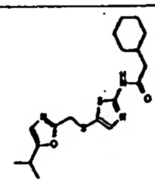
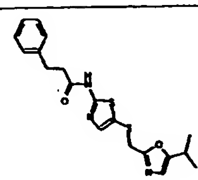
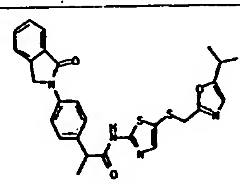
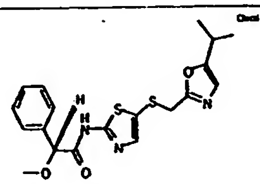
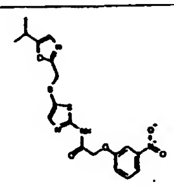
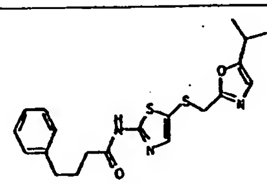
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 409 |  | C21 H22 N4 O2 S2 | 427 |
| 410 |  | C21 H26 N4 O2 S2 | 545 |
| 411 |  | C22 H24 N4 O2 S2 | 441 |
| 412 |  | C16 H19 N5 O2 S3 | 524 |
| 413 |  | C20 H23 N3 O3 S2 | 418 |
| 414 |  | C16 H19 N5 O2 S2 | 492 |
| 415 |  | C17 H19 N5 O4 S2 | 422 |
| 416 |  | C26 H34 N4 O4 S2 | 531 |

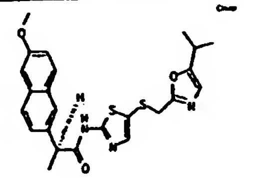
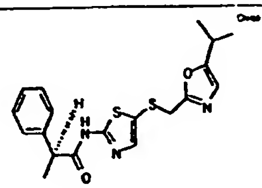
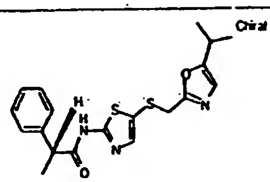
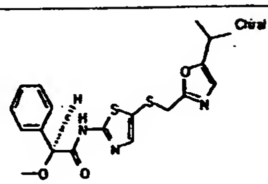
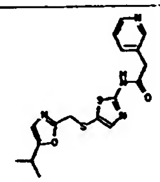
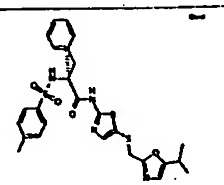
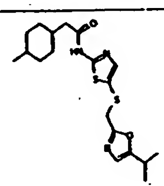
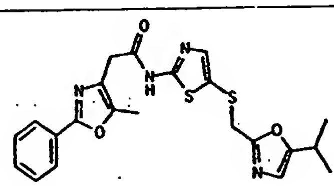
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 417 |  | C24 H30 N4 O4 S2 | 503 |
| 418 |  | C25 H32 N4 O4 S2 | 517 |
| 419 |  | C21 H26 N4 O2 S2 | 545 |
| 420 |  | C19 H22 N4 O2 S2 | 517 |
| 421 |  | C20 H24 N4 O2 S2 | 531 |
| 422 |  | C19 H22 N4 O2 S2 | 403 |
| 423 |  | C16 H14 F2 N4 O2 S2 | 397 |
| 424 |  | C16 H14 Cl2 N4 O2 S2 | 430 |

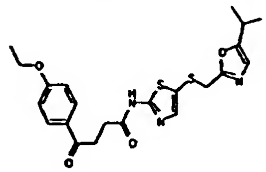
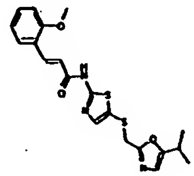
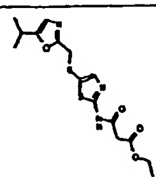
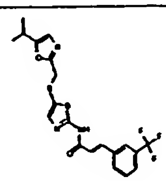
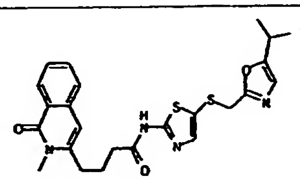
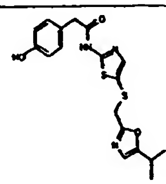
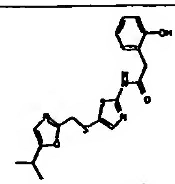
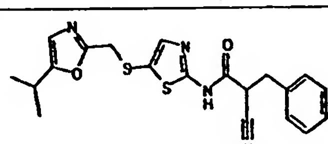
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 425 |  | C18 H20 N4 O S3 | 405 |
| 426 |  | C16 H14 Cl2 N4 O S3 | 446 |
| 427 |  | C21 H23 N3 O2 S2 | 414 |
| 428 |  | C19 H25 N3 O2 S2 | 392 |
| 429 |  | C22 H21 N3 O2 S2 | 424 |
| 430 |  | C22 H21 N3 O2 S2 | 424 |
| 431 |  | C15 H19 N3 O2 S2 | 338 |
| 432 |  | C16 H23 N3 O2 S2 | 354 |

| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 433 |  | C18 H19 N3 O2 S2 | 374 |
| 434 |  | C18 H16 N4 O2 S2 | 385 |
| 435 |  | C20 H23 N3 O2 S2 | 402 |
| 436 |  | C18 H17 F2 N3 O2 S2 | 410 |
| 437 |  | C21 H23 N3 O2 S2 | 414 |
| 438 |  | C18 H16 N4 O2 S3 | 417 |
| 439 |  | C19 H19 N3 O4 S2 | 418 |
| 440 |  | C20 H23 N3 O3 S2 | 418 |
| 441 |  | C18 H18 N4 O4 S2 | 419 |

| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 442 |  | C18 H18 N4 O4 S2 | 419 |
| 443 |  | C18 H18 N4 O4 S2 | 419 |
| 444 |  | C19 H21 N3 O4 S2 | 420 |
| 445 |  | C19 H21 N3 O4 S2 | 420 |
| 446 |  | C18 H19 N5 O2 S3 | 434 |
| 447 |  | C18 H19 N5 O2 S3 | 434 |
| 448 |  | C19 H18 F3 N3 O2 S2 | 442 |
| 449 |  | C18 H18 Br N3 O2 S2 | 453 |
| 450 |  | C21 H25 N3 O5 S2 | 464 |

| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 451 |  | C23 H28 N4 O4 S2 | 489 |
| 452 |  | C20 H21 N3 O2 S2 | 400 |
| 453 |  | C18 H25 N3 O2 S2 | 380 |
| 454 |  | C19 H21 N3 O2 S2 | 388 |
| 455 |  | C27 H26 N4 O3 S2 | 519 |
| 456 |  | C19 H21 N3 O3 S2 | 404 |
| 457 |  | C18 H18 N4 O5 S2 | 435 |
| 458 |  | C20 H23 N3 O2 S2 | 402 |

| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 459 |  | C24 H25 N3 O3 S2 | 468 |
| 460 |  | C19 H21 N3 O2 S2 | 388 |
| 461 |  | C19 H21 N3 O2 S2 | 388 |
| 462 |  | C19 H21 N3 O3 S2 | 404 |
| 463 |  | C17 H18 N4 O2 S2 | 489 |
| 464 |  | C26 H28 N4 O4 S3 | 557 |
| 465 |  | C19 H27 N3 O2 S2 | 394 |
| 466 |  | C22 H22 N4 O3 S2 | 455 |

| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 467 |  | C22 H25 N3 O4 S2 | 460 |
| 468 |  | C20 H21 N3 O3 S2 | 416 |
| 469 |  | C15 H19 N3 O4 S2 | 370 |
| 470 |  | C20 H18 F3 N3 O2 S2 | 454 |
| 471 |  | C24 H26 N4 O3 S2 | 483 |
| 472 |  | C18 H19 N3 O3 S2 | 390 |
| 473 |  | C18 H19 N3 O3 S2 | 390 |
| 474 |  | C20 H20 N4 O2 S2 | 413 |

C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

$C(NNO_2)$NH-alkyl, $C(NNO_2)$NH-cycloalkyl, $C(NNO_2)$NH-aryl, $C(NNO_2)$NH-alkyl-cycloalkyl, $C(NNO_2)$NH-alkyl-aryl, $C(NNO_2)$NH-heteroaryl, $C(NNO_2)$NH-alkyl-heteroaryl, $C(NNO_2)$NH-heterocyloalkyl, $C(NNO_2)$NH-alkyl-heterocycloalkyl; or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

$C(NOR_6)$NH-alkyl, $C(NOR_6)$NH-cycloalkyl, $C(NOR_6)$NH-aryl, $C(NOR_6)$NH-alkyl-cycloalkyl, $C(NOR_6)$NH-alkyl-aryl, $C(NOR_6)$NH-heteroaryl, $C(NOR_6)$NH-alkyl-heteroaryl, $C(NOR_6)$NH-heterocylcoalkyl, $C(NOR_6)$NH-alkyl-heterocycloalkyl;

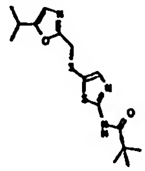
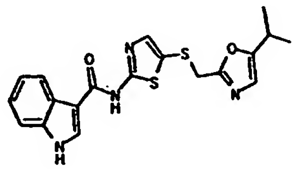
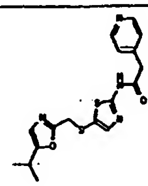
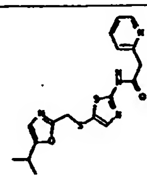
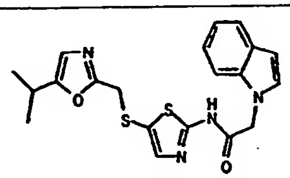
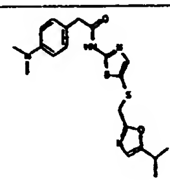
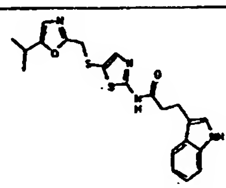
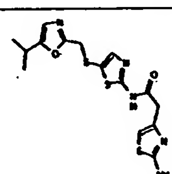
$R_5$ is hydrogen or alkyl;

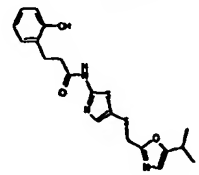
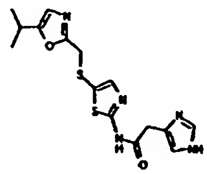
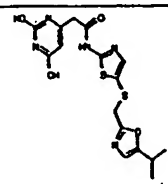
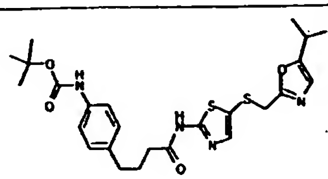
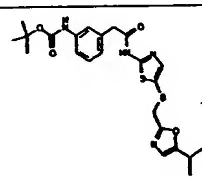
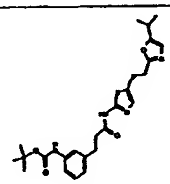
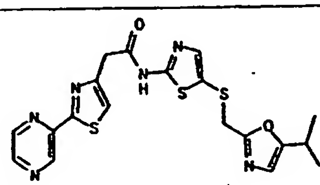
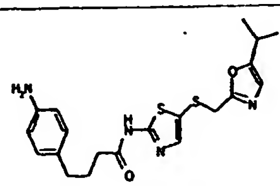
$R_6$ is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

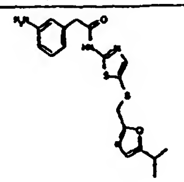
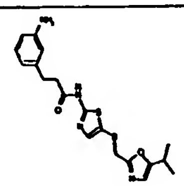
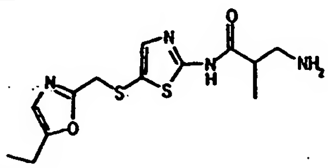
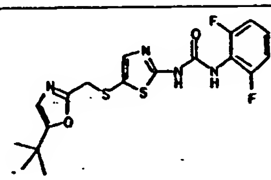
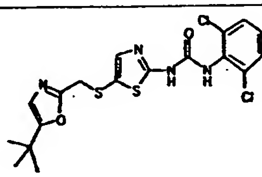
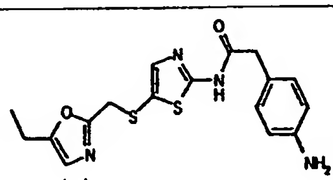
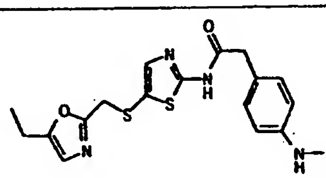
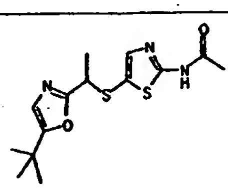
m is an integer of 0 to 2; and

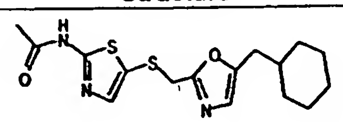
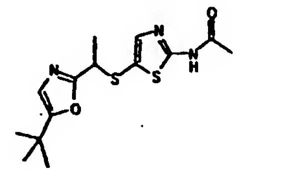
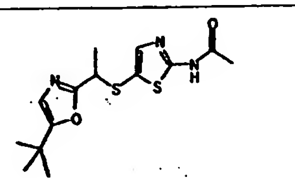
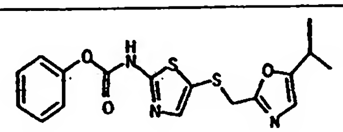
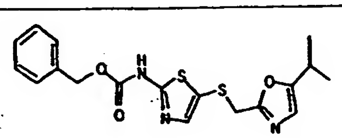
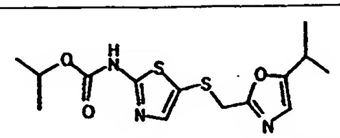
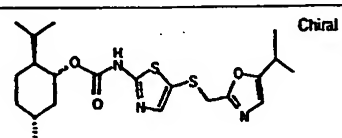
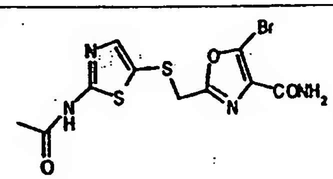
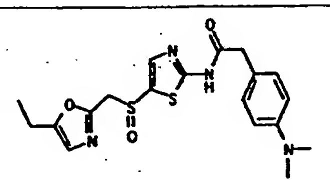
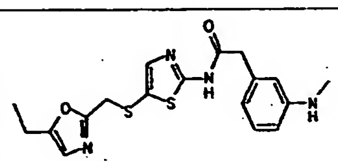
n is an integer of 1 to 3.

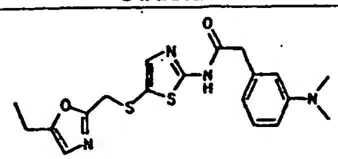
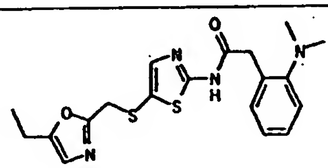
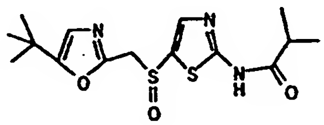
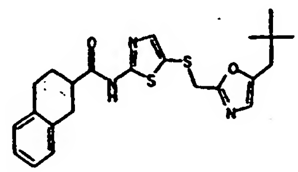
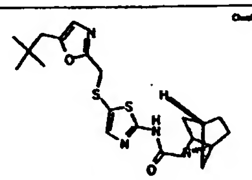
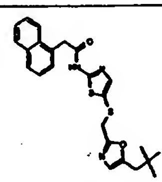
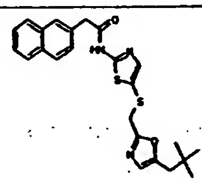
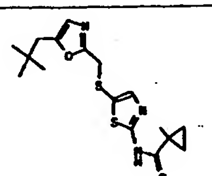
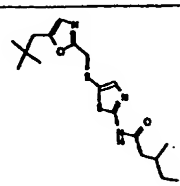
The compounds of formula I are protein kinase inhibitors and are useful in the treatment and prevention of proliferative diseases, for example, cancer, inflammation and arthritis. They may also be useful in the treatment of neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, viral diseases and fungal diseases.

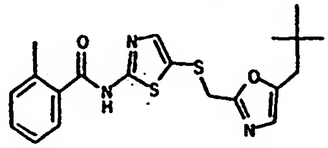
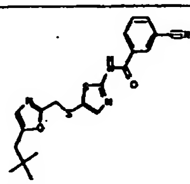
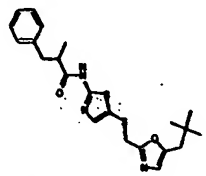
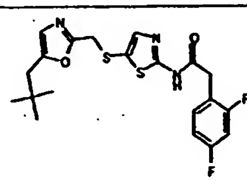
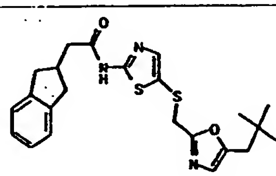
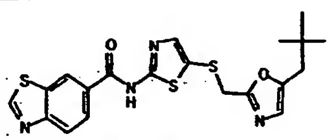
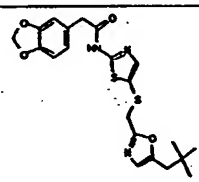
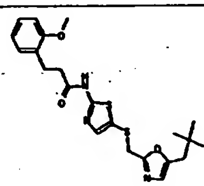
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 475 |  | C15 H21 N3 O2 S2 | 340 |
| 476 |  | C19 H18 N4 O2 S2 | 399 |
| 477 |  | C17 H18 N4 O2 S2 | 489 |
| 478 |  | C17 H18 N4 O2 S2 | 489 |
| 479 |  | C20 H20 N4 O2 S2 | 413 |
| 480 |  | C20 H24 N4 O2 S2 | 531 |
| 481 |  | C21 H22 N4 O2 S2 | 427 |
| 482 |  | C15 H17 N5 O2 S3 | 510 |

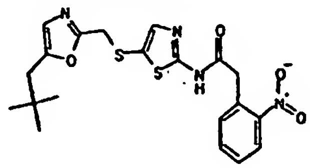
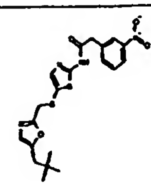
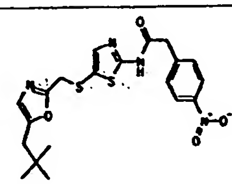
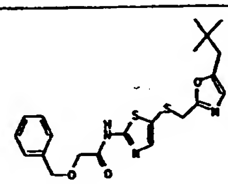
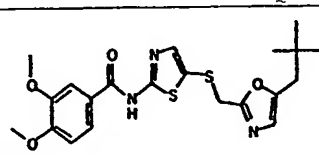
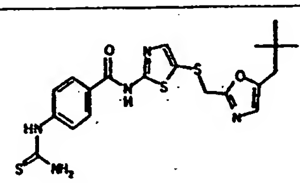
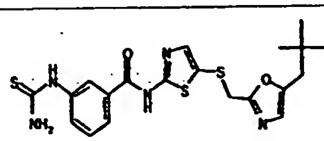
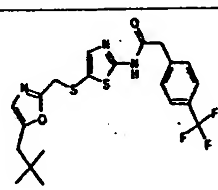
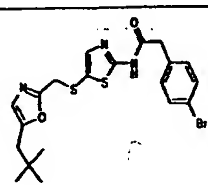
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 483 |  | C19 H21 N3 O3 S2 | 404 |
| 484 |  | C15 H17 N5 O2 S2 | 478 |
| 485 |  | C16 H17 N5 O4 S2 | 408 |
| 486 |  | C25 H32 N4 O4 S2 | 517 |
| 487 |  | C23 H28 N4 O4 S2 | 489 |
| 488 |  | C24 H30 N4 O4 S2 | 503 |
| 489 |  | C19 H18 N6 O2 S3 | 459 |
| 490 |  | C20 H24 N4 O2 S2 | 531 |

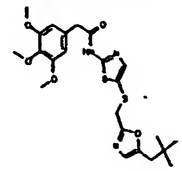
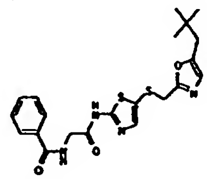
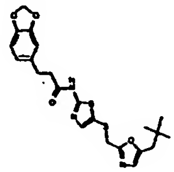
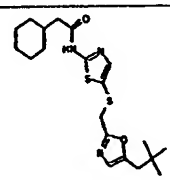
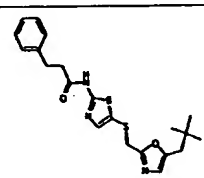
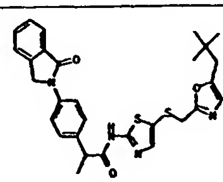
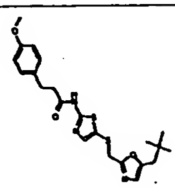
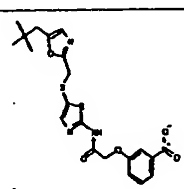
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 491 |  | C18 H20 N4 O2 S2 | 503 |
| 492 |  | C19 H22 N4 O2 S2 | 517 |
| 493 |  | C13 H18 N4 O2 S2 | 363 |
| 494 |  | C18 H18 F2 N4 O2 S2 | 425 |
| 495 |  | C18 H18 Cl2 N4 O2 S2 | 458 |
| 496 |  | C17 H18 N4 O2 S2 | 489 |
| 497 |  | C18 H20 N4 O2 S2 | 389 |
| 498 |  | C14 H19 N3 O2 S2 | 326 |

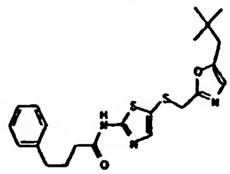
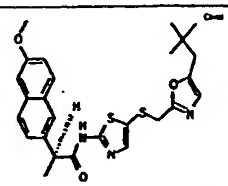
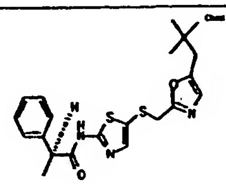
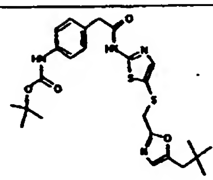
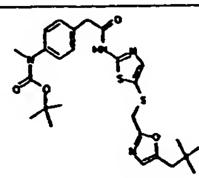
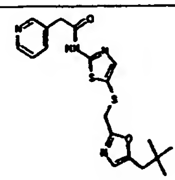
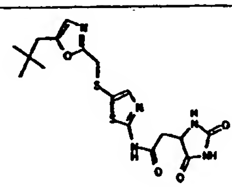
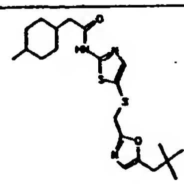
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 499 |  | C16 H21 N3 O2 S2 | 352 |
| 500 |  | C14 H19 N3 O2 S2 | 326 |
| 501 |  | C14 H19 N3 O2 S2 | 326 |
| 502 |  | C17 H17 N3 O3 S2 | 376 |
| 503 |  | C18 H19 N3 O3 S2 | 390 |
| 504 |  | C14 H19 N3 O3 S2 | 342 |
| 505 |  | C21 H31 N3 O3 S2 | 438 |
| 506 |  | C10 H9 Br N4 O3 S2 | 378 |
| 507 |  | C19 H22 N4 O3 S2 | 419 |
| 508 |  | C18 H20 N4 O2 S2 | 389 |

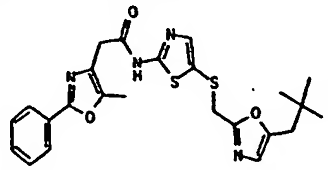
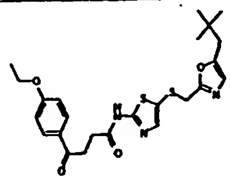
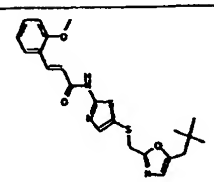
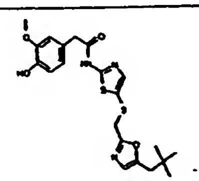
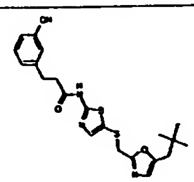
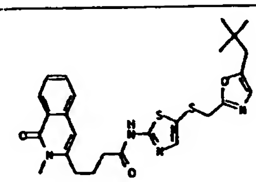
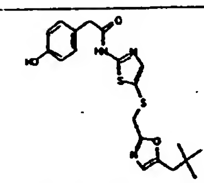
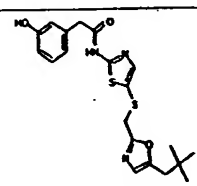
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 509 |  | C19 H22 N4 O2 S2 | 403 |
| 510 |  | C19 H22 N4 O2 S2 | 403 |
| 511 |  | C15 H21 N3 O3 S2 | 356 |
| 512 |  | C23 H27 N3 O2 S2 | 442 |
| 513 |  | C21 H29 N3 O2 S2 | 420 |
| 514 |  | C24 H25 N3 O2 S2 | 452 |
| 515 |  | C24 H25 N3 O2 S2 | 452 |
| 516 |  | C17 H23 N3 O2 S2 | 366 |
| 517 |  | C18 H27 N3 O2 S2 | 382 |

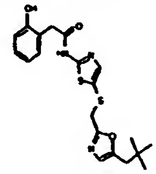
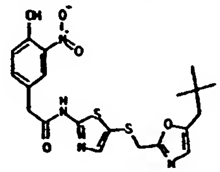
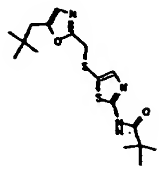
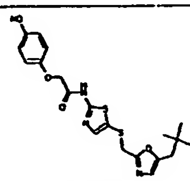
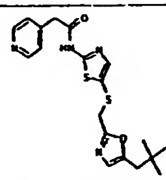
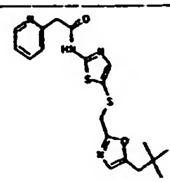
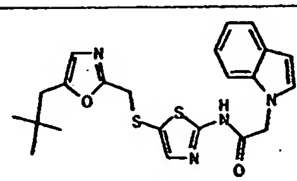
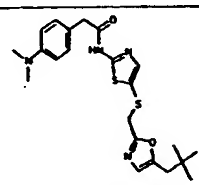
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 518 |  | C20 H23 N3 O2 S2 | 402 |
| 519 |  | C20 H20 N4 O2 S2 | 413 |
| 520 |  | C22 H27 N3 O2 S2 | 430 |
| 521 |  | C20 H21 F2 N3 O2 S2 | 438 |
| 522 |  | C23 H27 N3 O2 S2 | 442 |
| 523 |  | C20 H20 N4 O2 S3 | 445 |
| 524 |  | C21 H23 N3 O4 S2 | 446 |
| 525 |  | C22 H27 N3 O3 S2 | 446 |

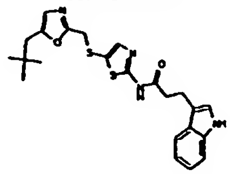
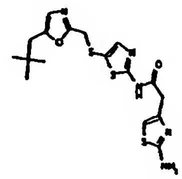
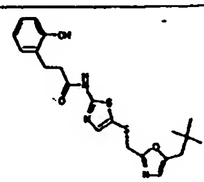
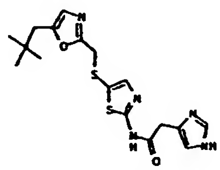
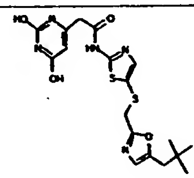
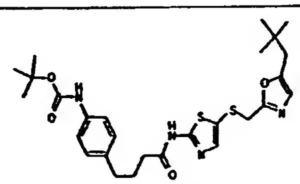
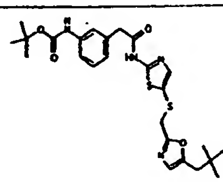
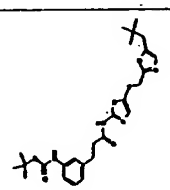
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 526 |  | C20 H22 N4 O4 S2 | 447 |
| 527 |  | C20 H22 N4 O4 S2 | 447 |
| 528 |  | C20 H22 N4 O4 S2 | 447 |
| 529 |  | C21 H25 N3 O3 S2 | 432 |
| 530 |  | C21 H25 N3 O4 S2 | 448 |
| 531 |  | C20 H23 N5 O2 S3 | 462 |
| 532 |  | C20 H23 N5 O2 S3 | 462 |
| 533 |  | C21 H22 F3 N3 O2 S2 | 470 |
| 534 |  | C20 H22 Br N3 O2 S2 | 481 |

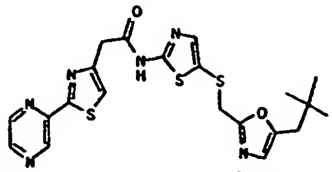
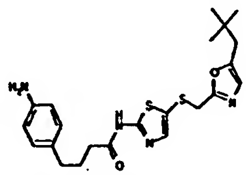
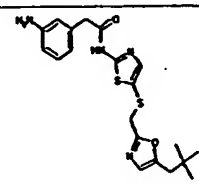
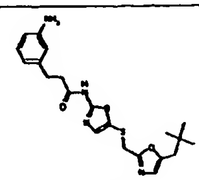
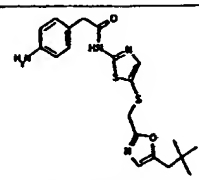
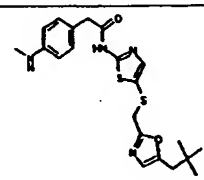
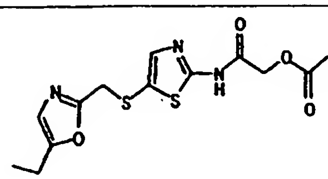
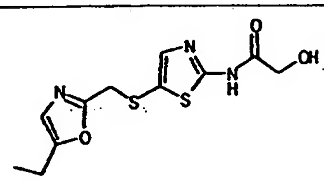
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 535 |  | C23 H29 N3 O5 S2 | 492 |
| 536 |  | C21 H24 N4 O3 S2 | 445 |
| 537 |  | C22 H25 N3 O4 S2 | 460 |
| 538 |  | C20 H29 N3 O2 S2 | 408 |
| 539 |  | C21 H25 N3 O2 S2 | 416 |
| 540 |  | C29 H30 N4 O3 S2 | 547 |
| 541 |  | C22 H27 N3 O3 S2 | 446 |
| 542 |  | C20 H22 N4 O5 S2 | 463 |

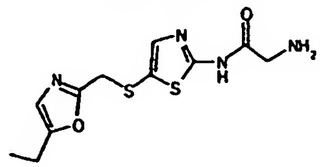
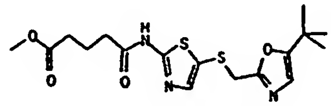
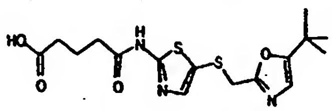
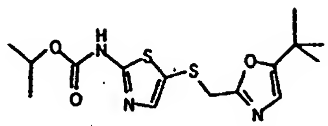
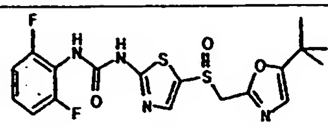
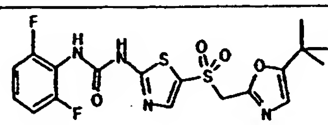
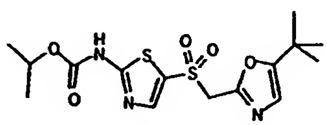
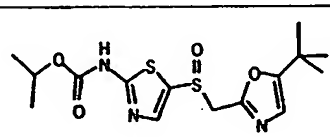
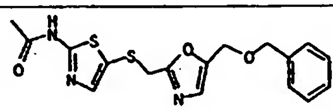
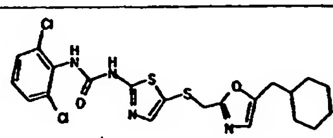
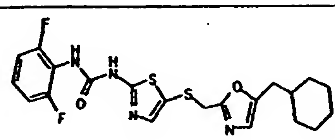
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 543 |  | C22 H27 N3 O2 S2 | 430 |
| 544 |  | C26 H29 N3 O3 S2 | 496 |
| 545 |  | C21 H25 N3 O2 S2 | 416 |
| 546 |  | C25 H32 N4 O4 S2 | 517 |
| 547 |  | C26 H34 N4 O4 S2 | 531 |
| 548 |  | C19 H22 N4 O2 S2 | 517 |
| 549 |  | C17 H21 N5 O4 S2 | 424 |
| 550 |  | C21 H31 N3 O2 S2 | 422 |

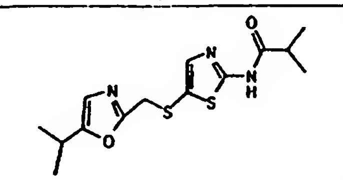
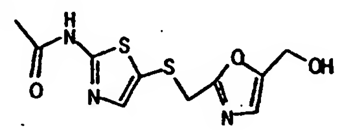
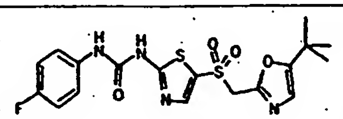
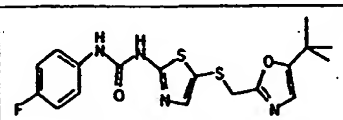
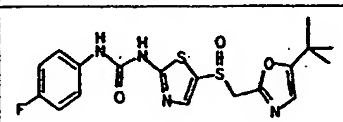
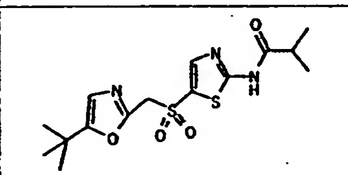
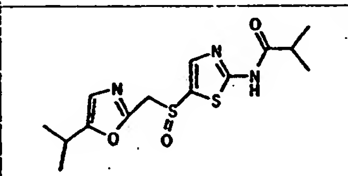
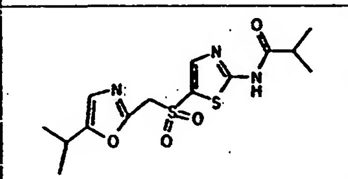
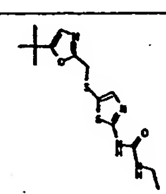
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 551 |  | C24 H26 N4 O3 S2 | 483 |
| 552 |  | C24 H29 N3 O4 S2 | 488 |
| 553 |  | C22 H25 N3 O3 S2 | 444 |
| 554 |  | C21 H25 N3 O4 S2 | 448 |
| 555 |  | C21 H25 N3 O3 S2 | 432 |
| 556 |  | C26 H30 N4 O3 S2 | 511 |
| 557 |  | C20 H23 N3 O3 S2 | 418 |
| 558 |  | C20 H23 N3 O3 S2 | 418 |

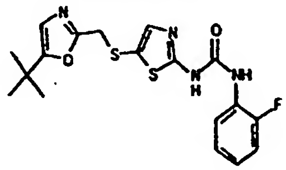
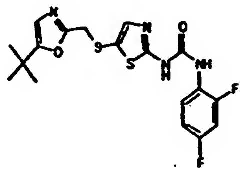
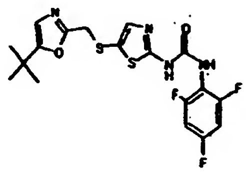
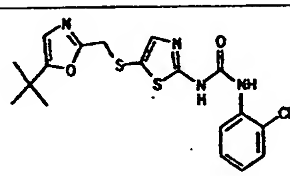
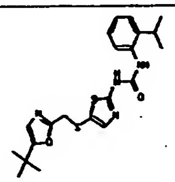
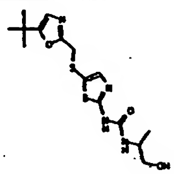
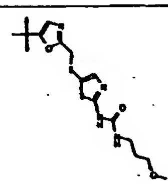
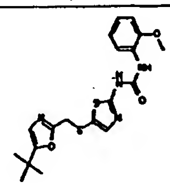
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 559 |  | C20 H23 N3 O3 S2 | 418 |
| 560 |  | C20 H22 N4 O5 S2 | 463 |
| 561 |  | C17 H25 N3 O2 S2 | 368 |
| 562 |  | C20 H23 N3 O4 S2 | 434 |
| 563 |  | C19 H22 N4 O2 S2 | 517 |
| 564 |  | C19 H22 N4 O2 S2 | 517 |
| 565 |  | C22 H24 N4 O2 S2 | 441 |
| 566 |  | C22 H28 N4 O2 S2 | 559 |

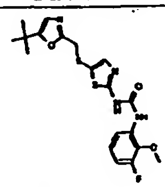
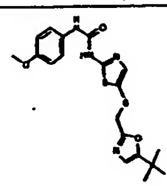
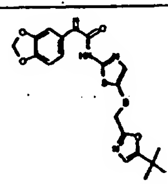
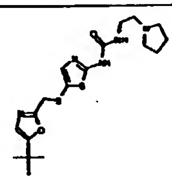
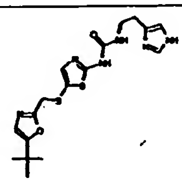
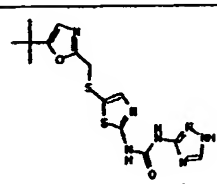
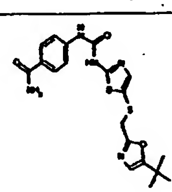
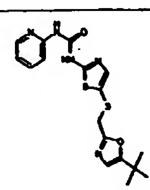
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 567 |  | C23 H26 N4 O2 S2 | 569 |
| 568 |  | C17 H21 N5 O2 S3 | 538 |
| 569 |  | C21 H25 N3 O3 S2 | 432 |
| 570 |  | C17 H21 N5 O2 S2 | 506 |
| 571 |  | C18 H21 N5 O4 S2 | 436 |
| 572 |  | C27 H36 N4 O4 S2 | 545 |
| 573 |  | C25 H32 N4 O4 S2 | 517 |
| 574 |  | C26 H34 N4 O4 S2 | 531 |

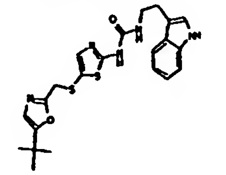
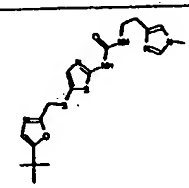
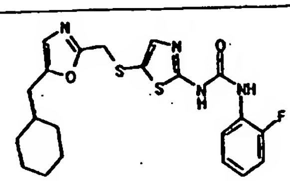
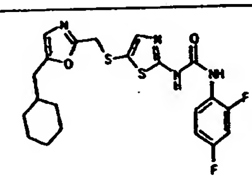
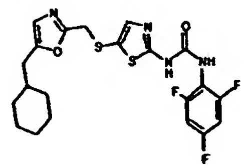
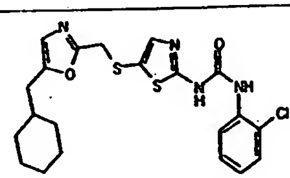
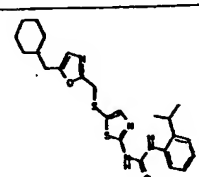
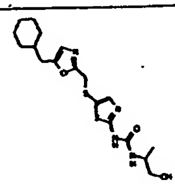
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 575 |  | C21 H22 N6 O2 S3 | 487 |
| 576 |  | C22 H28 N4 O2 S2 | 559 |
| 577 |  | C20 H24 N4 O2 S2 | 531 |
| 578 |  | C21 H26 N4 O2 S2 | 545 |
| 579 |  | C20 H24 N4 O2 S2 | 531 |
| 580 |  | C21 H26 N4 O2 S2 | 545 |
| 581 |  | C13 H15 N3 O4 S2 | 342 |
| 582 |  | C11 H13 N3 O3 S2 | 300 |

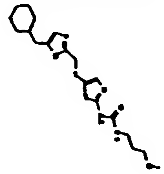
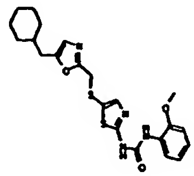
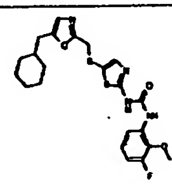
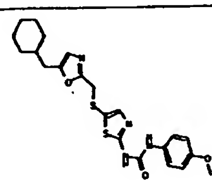
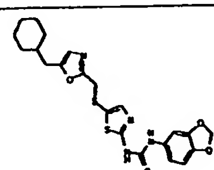
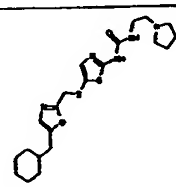
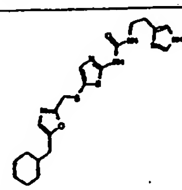
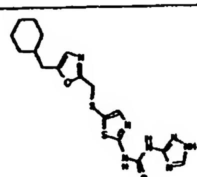
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 583 |  | C11 H14 N4 O2 S2 | 413 |
| 584 |  | C17 H23 N3 O4 S2 | 398 |
| 585 |  | C16 H21 N3 O4 S2 | 384 |
| 586 |  | C15 H21 N3 O3 S2 | 356 |
| 587 |  | C18 H18 F2 N4 O3 S2 | 441 |
| 588 |  | C18 H18 F2 N4 O4 S2 | 457 |
| 589 |  | C15 H21 N3 O5 S2 | 388 |
| 590 |  | C15 H21 N3 O4 S2 | 372 |
| 591 |  | C17 H17 N3 O3 S2 | 376 |
| 592 |  | C21 H22 Cl2 N4 O2 S2 | 498 |
| 593 |  | C21 H22 F2 N4 O2 S2 | 465 |

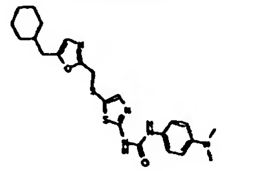
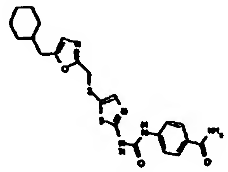
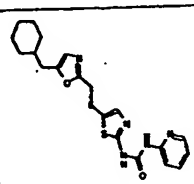
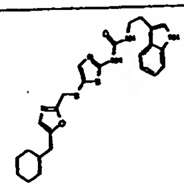
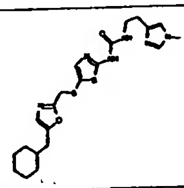
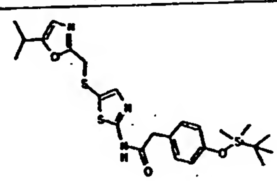
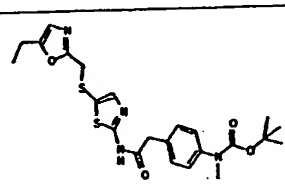
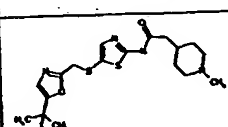
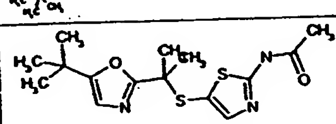
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 594 |  | C14 H19 N3 O2 S2 | 326 |
| 595 |  | C10 H11 N3 O3 S2 | 286 |
| 596 |  | C18 H19 F N4 O4 S2 | 439 |
| 597 |  | C18 H19 F N4 O2 S2 | 407 |
| 598 |  | C18 H19 F N4 O3 S2 | 423 |
| 599 |  | C15 H21 N3 O4 S2 | 372 |
| 600 |  | C14 H19 N3 O3 S2 | 342 |
| 601 |  | C14 H19 N3 O4 S2 | 358 |
| 602 |  | C14 H20 N4 O2 S2 | 341 |

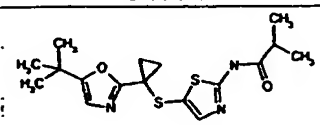
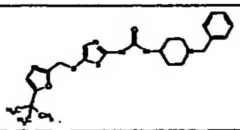
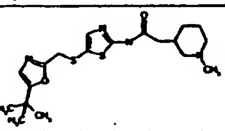
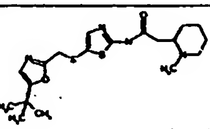
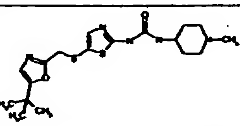
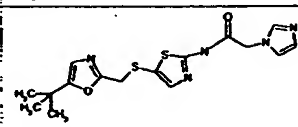
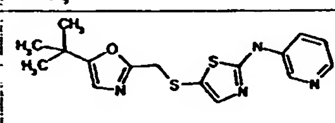
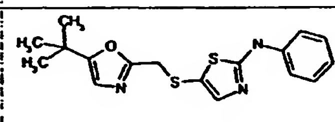
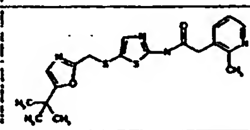
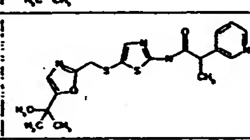
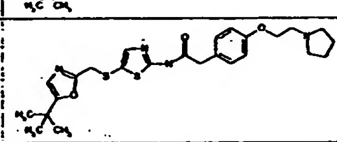
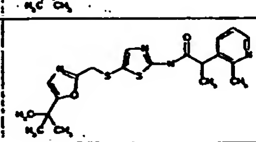
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 603 |  | C18 H19 F N4 O2 S2 | 407 |
| 604 |  | C18 H18 F2 N4 O2 S2 | 425 |
| 605 |  | C18 H17 F3 N4 O2 S2 | 443 |
| 606 |  | C18 H19 Cl N4 O2 S2 | 423 |
| 607 |  | C21 H26 N4 O2 S2 | 431 |
| 608 |  | C15 H22 N4 O3 S2 | 371 |
| 609 |  | C16 H24 N4 O3 S2 | 385 |
| 610 |  | C19 H22 N4 O3 S2 | 419 |

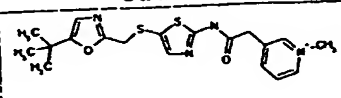
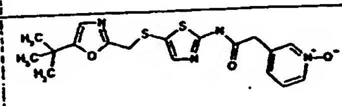
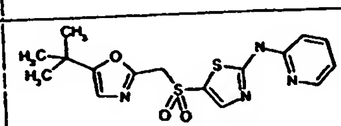
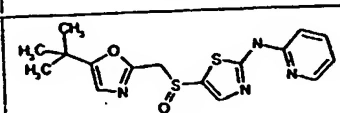
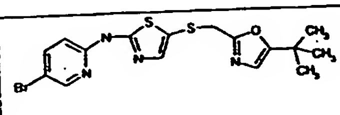
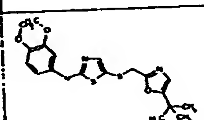
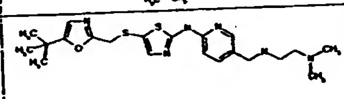
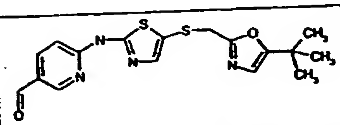
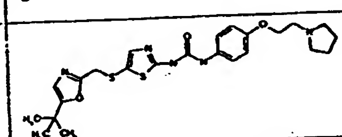
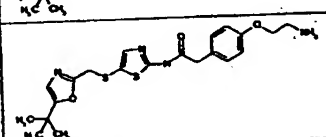
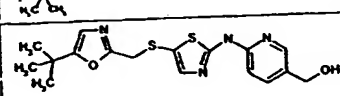
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 611 |  | C19 H21 F N4 O3 S2 | 437 |
| 612 |  | C19 H22 N4 O3 S2 | 419 |
| 613 |  | C19 H20 N4 O4 S2 | 433 |
| 614 |  | C18 H27 N5 O2 S2 | 524 |
| 615 |  | C17 H22 N6 O2 S2 | 521 |
| 616 |  | C14 H17 N7 O2 S2 | 494 |
| 617 |  | C19 H21 N5 O3 S2 | 432 |
| 618 |  | C17 H19 N5 O2 S2 | 504 |

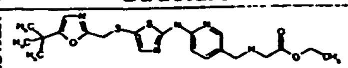
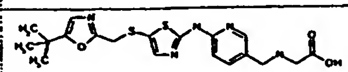
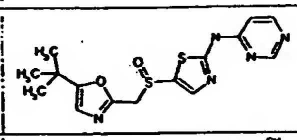
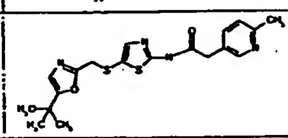
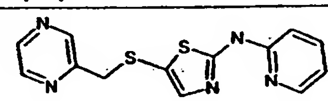
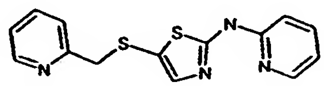
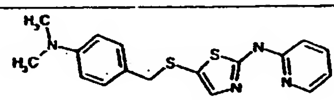
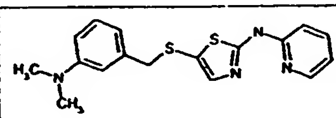
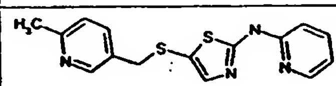
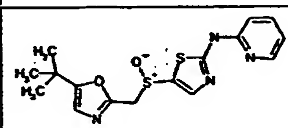
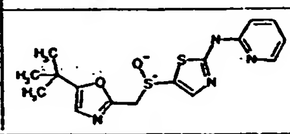
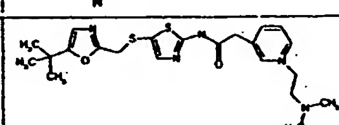
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 619 |  | C22 H25 N5 O2 S2 | 456 |
| 620 |  | C18 H24 N6 O2 S2 | 535 |
| 621 |  | C21 H23 F N4 O2 S2 | 447 |
| 622 |  | C21 H22 F2 N4 O2 S2 | 465 |
| 623 |  | C21 H21 F3 N4 O2 S2 | 483 |
| 624 |  | C21 H23 Cl N4 O2 S2 | 464 |
| 625 |  | C24 H30 N4 O2 S2 | 471 |
| 626 |  | C18 H26 N4 O3 S2 | 411 |

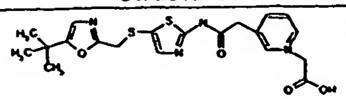
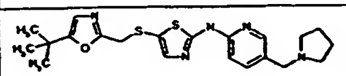
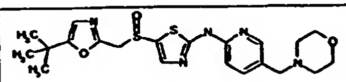
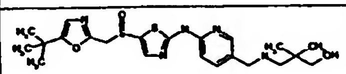
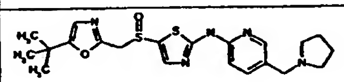
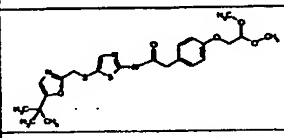
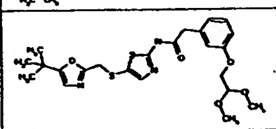
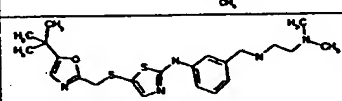
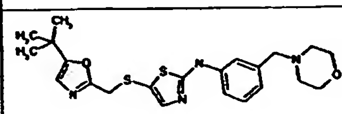
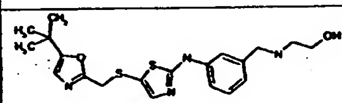
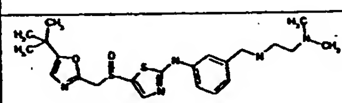
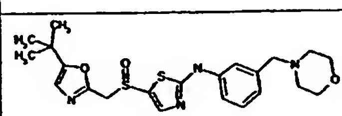
| Example | Structure | Molecular Formula | (M+H)+ |
| --- | --- | --- | --- |
| 627 |  | C19 H28 N4 O3 S2 | 425 |
| 628 |  | C22 H26 N4 O3 S2 | 459 |
| 629 |  | C22 H25 F N4 O3 S2 | 477 |
| 630 |  | C22 H26 N4 O3 S2 | 459 |
| 631 |  | C22 H24 N4 O4 S2 | 473 |
| 632 |  | C21 H31 N5 O2 S2 | 564 |
| 633 |  | C20 H26 N6 O2 S2 | 561 |
| 634 |  | C17 H21 N7 O2 S2 | 534 |

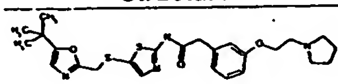
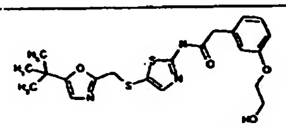
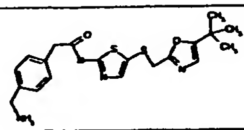
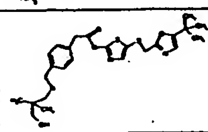
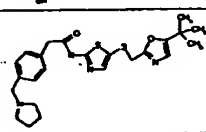
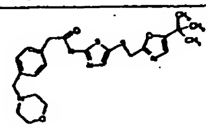
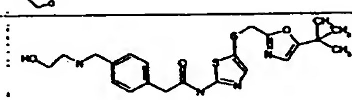
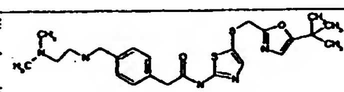
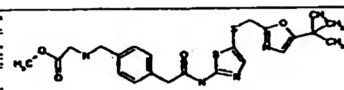
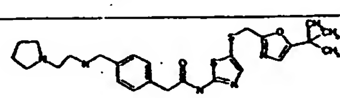
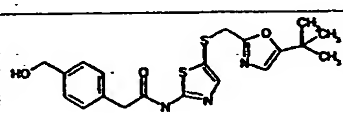
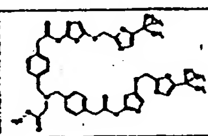
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 635 |  | C23 H29 N5 O2 S2 | 586 |
| 636 |  | C22 H25 N5 O3 S2 | 472 |
| 637 |  | C20 H23 N5 O2 S2 | 544 |
| 638 |  | C25 H29 N5 O2 S2 | 496 |
| 639 |  | C21 H28 N6 O2 S2 | 575 |
| 640 |  | C24 H33 N3 O3 S2 Si | 504 |
| 641 |  | C23 H28 N4 O4 S2 | 489 |
| 642 |  | C19 H28 N4 O2 S2 | 409 |
| 643 |  | C15 H21 N3 O2 S2 | 340 |

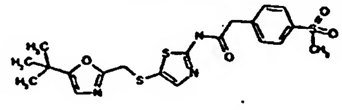
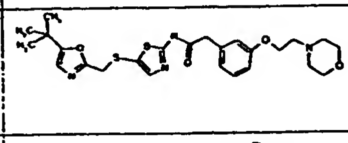
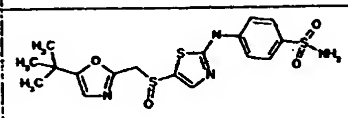
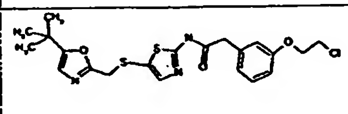
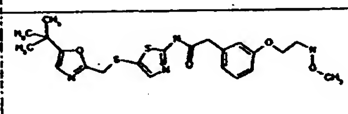
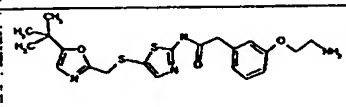
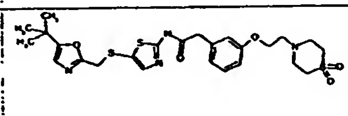
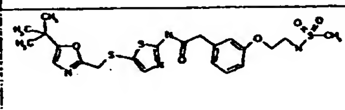
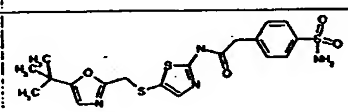
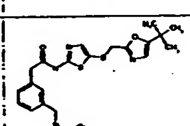
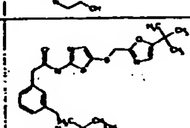
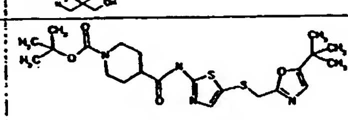
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 644 |  | C17 H23 N3 O2 S2 | 367 |
| 645 |  | C24 H31 N5 O2 S2 | 487 |
| 646 |  | C19 H28 N4 O2 S2 | 410 |
| 647 |  | C19 H28 N4 O2 S2 | 410 |
| 648 |  | C18 H27 N5 O2 S2 | 411 |
| 649 |  | C16 H19 N5 O2 S2 | 378 |
| 650 |  | C16 H18 N4 O S2 | 347 |
| 651 |  | C17 H19 N3 O S2 | 346 |
| 652 |  | C19 H22 N4 O2 S2 | 404 |
| 653 |  | C19 H22 N4 O2 S2 | 404 |
| 654 |  | C25 H32 N4 O3 S2 | 502 |
| 655 |  | C20 H24 N4 O2 S2 | 418 |

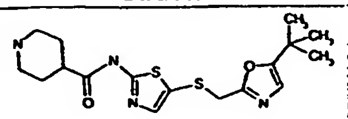
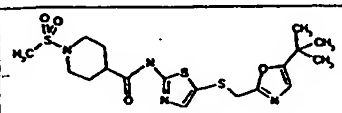
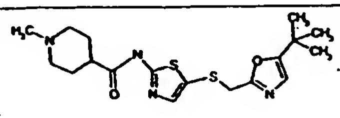
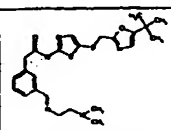
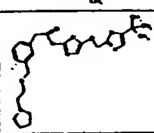
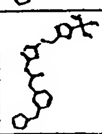
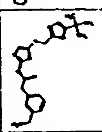
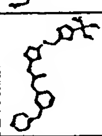
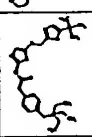
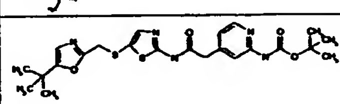
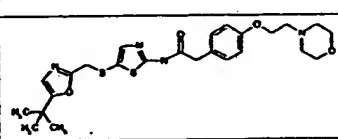
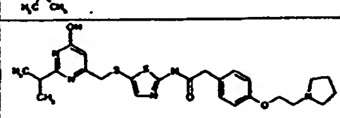
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 656 |  | C19 H23 N4 O2 S2 | 405 |
| 657 |  | C18 H20 N4 O3 S2 | 406 |
| 658 |  | C16 H18 N4 O3 S2 | 379 |
| 659 |  | C16 H18 N4 O2 S2 | 363 |
| 660 |  | C16 H17 Br N4 O S2 | 426 |
| 661 |  | C19 H23 N3 O3 S2 | 407 |
| 662 |  | C21 H30 N6 O S2 | 448 |
| 663 |  | C19 H25 N5 O2 S2 | 421 |
| 664 |  | C17 H18 N4 O2 S2 | 375 |
| 665 |  | C24 H31 N5 O3 S2 | 503 |
| 666 |  | C21 H26 N4 O3 S2 | 448 |
| 667 |  | C17 H20 N4 O2 S2 | 378 |

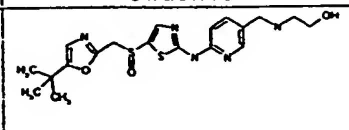
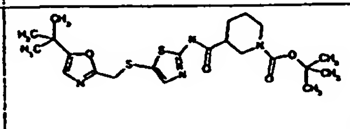
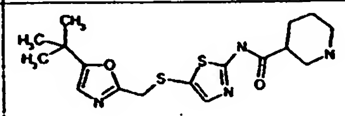
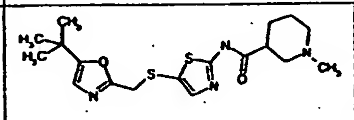
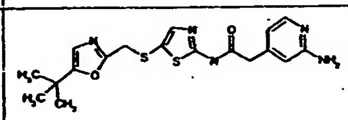
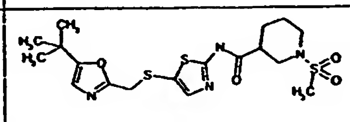
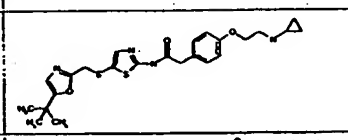
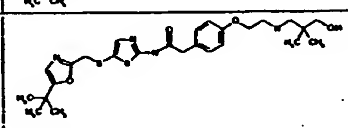
| Example | Structure | Molecular Formula | (M+H)+ |
| --- | --- | --- | --- |
| 668 |  | C21 H27 N5 O3 S2 | 463 |
| 669 |  | C19 H23 N5 O3 S2 | 435 |
| 670 |  | C15 H17 N5 O2 S2 | 364 |
| 671 |  | C19 H22 N4 O2 S2 | 404 |
| 672 |  | C13 H11 N5 S2 | 302 |
| 673 |  | C14 H12 N4 S2 | 301 |
| 674 |  | C17 H18 N4 S2 | 343 |
| 675 |  | C17 H18 N4 S2 | 343 |
| 676 |  | C15 H14 N4 S2 | 315 |
| 677 |  | C16 H18 N4 O2 S2 | 363 |
| 678 |  | C16 H18 N4 O2 S2 | 363 |
| 679 |  | C22 H31 N5 O2 S2 | 463 |

| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 680 |  | C20 H24 N4 O4 S2 | 450 |
| 681 |  | C21 H27 N5 O S2 | 431 |
| 682 |  | C21 H27 N5 O3 S2 | 463 |
| 683 |  | C22 H31 N5 O3 S2 | 479 |
| 684 |  | C21 H27 N5 O2 S2 | 447 |
| 685 |  | C23 H29 N3 O5 S2 | 493 |
| 686 |  | C23 H29 N3 O5 S2 | 493 |
| 687 |  | C22 H31 N5 O S2 | 447 |
| 688 |  | C22 H28 N4 O2 S2 | 446 |
| 689 |  | C20 H26 N4 O2 S2 | 420 |
| 690 |  | C22 H31 N5 O2 S2 | 463 |
| 691 |  | C22 H28 N4 O3 S2 | 462 |

| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 692 |  | C25 H32 N4 O3 S2 | 502 |
| 693 |  | C21 H25 N3 O4 S2 | 449 |
| 694 |  | C20 H24 N4 O2 S2 | 418 |
| 695 |  | C25 H34 N4 O3 S2 | 504 |
| 696 |  | C24 H30 N4 O2 S2 | 472 |
| 697 |  | C24 H30 N4 O3 S2 | 488 |
| 698 |  | C22 H28 N4 O3 S2 | 462 |
| 699 |  | C24 H33 N5 O2 S2 | 489 |
| 700 |  | C23 H28 N4 O4 S2 | 490 |
| 701 |  | C26 H35 N5 O2 S2 | 515 |
| 702 |  | C20 H23 N3 O3 S2 | 419 |
| 703 |  | C43 H49 N7 O6 S4 | 889 |

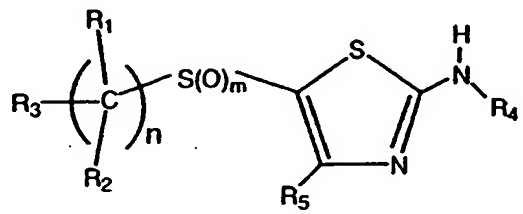
| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 704 |  | C20 H23 N3 O4 S3 | 467 |
| 705 |  | C25 H32 N4 O4 S2 | 518 |
| 706 |  | C17 H20 N4 O4 S3 | 442 |
| 707 |  | C21 H24 Cl N3 O3 S2 | 467 |
| 708 |  | C22 H28 N4 O4 S2 | 478 |
| 709 |  | C21 H26 N4 O3 S2 | 448 |
| 710 |  | C25 H32 N4 O5 S3 | 566 |
| 711 |  | C22 H28 N4 O5 S3 | 526 |
| 712 |  | C19 H22 N4 O4 S3 | 468 |
| 713 |  | C22 H28 N4 O3 S2 | 462 |
| 714 |  | C25 H34 N4 O3 S2 | 504 |
| 715 |  | C22 H32 N4 O4 S2 | 482 |

| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 716 |  | C17 H24 N4 O2 S2 | 382 |
| 717 |  | C18 H26 N4 O4 S3 | 460 |
| 718 |  | C18 H26 N4 O2 S2 | 396 |
| 719 |  | C24 H33 N5 O2 S2 | 489 |
| 720 |  | C26 H35 N5 O2 S2 | 515 |
| 721 |  | C24 H30 N4 O2 S2 | 472 |
| 722 |  | C20 H24 N4 O2 S2 | 418 |
| 723 |  | C24 H30 N4 O3 S2 | 488 |
| 724 |  | C26 H38 N4 O2 S2 | 504 |
| 725 |  | C23 H29 N5 O4 S2 | 505 |
| 726 |  | C25 H32 N4 O4 S2 | 518 |
| 727 |  | C25 H31 N5 O3 S2 | 515 |

| Example | Structure | Molecular Formula | (M+H)+ |
|---|---|---|---|
| 728 |  | C19 H25 N5 O3 S2 | 437 |
| 729 |  | C22 H32 N4 O4 S2 | 482 |
| 730 |  | C17 H24 N4 O2 S2 | 382 |
| 731 |  | C18 H26 N4 O2 S2 | 396 |
| 732 |  | C18 H21 N5 O2 S2 | 405 |
| 733 |  | C18 H26 N4 O4 S3 | 460 |
| 734 |  | C24 H30 N4 O3 S2 | 488 |
| 735 |  | C26 H36 N4 O4 S2 | 534 |

**What is Claimed is:**

1. A compound of the formula



(I)

and pharmaceutically acceptable salts thereof wherein:

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is aryl or heteroaryl;

$R_4$ is alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

$SO_2$-cycloalkyl, $SO_2$-aryl, $SO_2$-alkyl-cycloalkyl, $SO_2$-alkyl-aryl, $SO_2$-heteroaryl, $SO_2$-alkyl-heteroaryl, $SO_2$-heterocycloalkyl, $SO_2$-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

C($NNO_2$)NH-alkyl, C($NNO_2$)NH-cycloalkyl, C($NNO_2$)NH-aryl, C($NNO_2$)NH-alkyl-cycloalkyl, C($NNO_2$)NH-alkyl-aryl, C($NNO_2$)NH-heteroaryl, C($NNO_2$)NH-alkyl-heteroaryl, C($NNO_2$)NH-heterocyloalkyl, C($NNO_2$)NH-alkyl-heterocycloalkyl; or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

C($NOR_6$)NH-alkyl, C($NOR_6$)NH-cycloalkyl, C($NOR_6$)NH-aryl, C($NOR_6$)NH-alkyl-cycloalkyl, C($NOR_6$)NH-alkyl-aryl, C($NOR_6$)NH-heteroaryl, C($NOR_6$)NH-alkyl-heteroaryl, C($NOR_6$)NH-heterocylcoalkyl, C($NOR_6$)NH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen or alkyl;

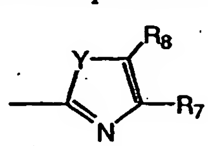
$R_6$ is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

m is an integer of 0 to 2; and

n is an integer of 1 to 3.

2. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 


wherein Y is oxygen, sulfur or $NR_9$

$R_4$ is alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl,

heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

$SO_2$-cycloalkyl, $SO_2$-aryl, $SO_2$-alkyl-cycloalkyl, $SO_2$-alkyl-aryl, $SO_2$-heteroaryl, $SO_2$-alkyl-heteroaryl, $SO_2$-heterocycloalkyl, $SO_2$-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

C($NNO_2$)NH-alkyl, C($NNO_2$)NH-cycloalkyl, C($NNO_2$)NH-aryl, C($NNO_2$)NH-alkyl-cycloalkyl, C($NNO_2$)NH-alkyl-aryl, C($NNO_2$)NH-heteroaryl, C($NNO_2$)NH-alkyl-heteroaryl, C($NNO_2$)NH-heterocyloalkyl, C($NNO_2$)NH-alkyl-heterocycloalkyl;

or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl,

C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

C($NOR_6$)NH-alkyl, C($NOR_6$)NH-cycloalkyl, C($NOR_6$)NH-aryl, C($NOR_6$)NH-alkyl-cycloalkyl, C($NOR_6$)NH-alkyl-aryl, C($NOR_6$)NH-heteroaryl, C($NOR_6$)NH-alkyl-heteroaryl, C($NOR_6$)NH-heterocylcoalkyl, C($NOR_6$)NH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen or alkyl;

$R_6$ is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

$R_7$ and $R_8$ are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, subsituted aryl, cycloalkylalkyl, arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

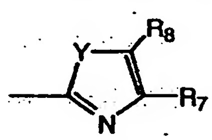
$R_9$ is hydrogen, alkyl, cycloalkyl, aryl, akylcycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

m is an integer of 0 to 2; and

n is an integer of 1 to 3.

3. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is oxygen;

$R_4$ is alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

$SO_2$-cycloalkyl, $SO_2$-aryl, $SO_2$-alkyl-cycloalkyl, $SO_2$-alkyl-aryl, $SO_2$-heteroaryl, $SO_2$-alkyl-heteroaryl, $SO_2$-heterocycloalkyl, $SO_2$-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

C($NNO_2$)NH-alkyl, C($NNO_2$)NH-cycloalkyl, C($NNO_2$)NH-aryl, C($NNO_2$)NH-alkyl-cycloalkyl, C($NNO_2$)NH-alkyl-aryl, C($NNO_2$)NH-heteroaryl, C($NNO_2$)NH-alkyl-heteroaryl, C($NNO_2$)NH-heterocyloalkyl, C($NNO_2$)NH-alkyl-heterocycloalkyl; or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

C($NOR_6$)NH-alkyl, C($NOR_6$)NH-cycloalkyl, C($NOR_6$)NH-aryl, C($NOR_6$)NH-alkyl-cycloalkyl, C($NOR_6$)NH-alkyl-aryl, C($NOR_6$)NH-heteroaryl, C($NOR_6$)NH-alkyl-heteroaryl,

C(NOR$_6$)NH-heterocylcoalkyl, C(NOR$_6$)NH-alkyl-heterocycloalkyl;

R$_5$ is hydrogen;

R$_6$ is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

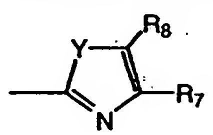
R$_7$ and R$_8$ are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, subsituted aryl, cycloalkylalkyl, arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

m is an integer of 0 to 2; and

n is an integer of 1 to 3.

4. The compounds as recited in Claim 1, wherein

R$_1$ and R$_2$ are independently hydrogen, fluorine or alkyl;

R$_3$ is 

wherein Y is sulfur;

R$_4$ is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

SO$_2$-cycloalkyl, SO$_2$-aryl, SO$_2$-alkyl-cycloalkyl, SO$_2$-alkyl-aryl,

$SO_2$-heteroaryl, $SO_2$-alkyl-heteroaryl, $SO_2$-heterocycloalkyl, $SO_2$-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

C($NNO_2$)NH-alkyl, C($NNO_2$)NH-cycloalkyl, C($NNO_2$)NH-aryl, C($NNO_2$)NH-alkyl-cycloalkyl, C($NNO_2$)NH-alkyl-aryl, C($NNO_2$)NH-heteroaryl, C($NNO_2$)NH-alkyl-heteroaryl, C($NNO_2$)NH-heterocyloalkyl, C($NNO_2$)NH-alkyl-heterocycloalkyl; or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

C($NOR_6$)NH-alkyl, C($NOR_6$)NH-cycloalkyl, C($NOR_6$)NH-aryl, C($NOR_6$)NH-alkyl-cycloalkyl, C($NOR_6$)NH-alkyl-aryl, C($NOR_6$)NH-heteroaryl, C($NOR_6$)NH-alkyl-heteroaryl, C($NOR_6$)NH-heterocylcoalkyl, C($NOR_6$)NH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

$R_6$ is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

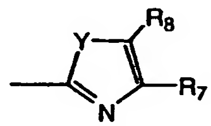
$R_7$ and $R_8$ are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, subsituted aryl, cycloalkylalkyl, arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

m is an integer of 0 to 2; and

n is an integer of 1 to 3.

5. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is $NR_9$;

$R_4$ is alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

$SO_2$-cycloalkyl, $SO_2$-aryl, $SO_2$-alkyl-cycloalkyl, $SO_2$-alkyl-aryl, $SO_2$-heteroaryl, $SO_2$-alkyl-heteroaryl, $SO_2$-heterocycloalkyl, $SO_2$-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

$C(NNO_2)$NH-alkyl, $C(NNO_2)$NH-cycloalkyl, $C(NNO_2)$NH-aryl, $C(NNO_2)$NH-alkyl-cycloalkyl, $C(NNO_2)$NH-alkyl-aryl,

$C(NNO_2)NH$-heteroaryl, $C(NNO_2)NH$-alkyl-heteroaryl, $C(NNO_2)NH$-heterocyloalkyl, $C(NNO_2)NH$-alkyl-heterocycloalkyl;

or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

$C(NOR_6)NH$-alkyl, $C(NOR_6)NH$-cycloalkyl, $C(NOR_6)NH$-aryl, $C(NOR_6)NH$-alkyl-cycloalkyl, $C(NOR_6)NH$-alkyl-aryl, $C(NOR_6)NH$-heteroaryl, $C(NOR_6)NH$-alkyl-heteroaryl, $C(NOR_6)NH$-heterocylcoalkyl, $C(NOR_6)NH$-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

$R_6$ is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

$R_7$ and $R_8$ are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, subsituted aryl, cycloalkylalkyl, arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

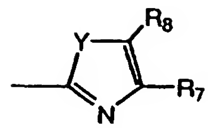
$R_9$ is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

m is an integer of 0 to 2; and

n is an integer of 1 to 3.

6. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is oxygen;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-cycloalkyl, CO-alkyl-heteroaryl, CO-alkyl-heteroalkyl, CO-alkyl-heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen; and

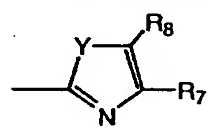
$R_7$ and $R_8$ are hydrogen;

m is the integer 0; and

n is the integer 1.

7. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is oxygen;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

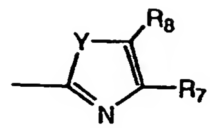
$R_7$ and $R_8$ are alkyl;

m is the integer 0; and

n is the integer 1.

8. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is oxygen;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

$R_7$ is hydrogen;

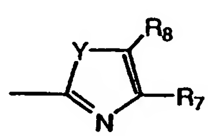
$R_8$ is alkyl;

m is the integer 0; and

n is the integer 1.

9. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is oxygen;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

$R_7$ is alkyl;

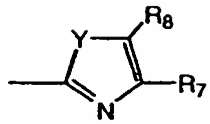
$R_8$ is hydrogen;

m is the integer 0; and

n is the integer 1.

10. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is sulfur;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

$R_7$ is hydrogen;

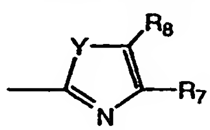
$R_8$ is alkyl;

m is the integer 0; and

n is the integer 1

11. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is sulfur;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

$R_7$ is alkyl;

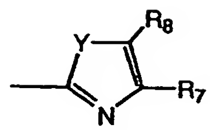
$R_8$ is hydrogen;

m is the integer 0; and

n is the integer 1.

12. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is $NR_9$;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

$R_7$ is hydrogen;

$R_8$ is alkyl;

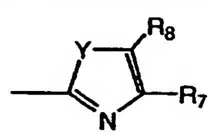
$R_9$ is hydrogen, alkyl, cycloalkyl, aryl, alkyl-cycloalkyl, alkyl-aryl, heteroaryl, alkyl-heteroaryl, heterocycloalkyl, or alkyl-heterocycloalkyl;

m is the integer 0; and

n is the integer 1.

13. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein Y is $NR_9$;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

$R_7$ is alkyl;

$R_8$ is hydrogen;

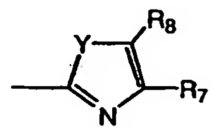
$R_9$ is alkyl;

m is the integer 0; and

n is the integer 1.

14. The compounds as recited in Claim 1, wherein

$R_1$ and $R_2$ are independently hydrogen, fluorine or alkyl;

$R_3$ is 

wherein X is $NR_9$;

$R_4$ is CO-alkyl, CO-alkyl-aryl, CO-cycloalkyl, CO-alkyl-heteroaryl, CO-alkyl-heteroalkyl, CO-alkyl-heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

$R_5$ is hydrogen;

$R_7$ is alkyl;

$R_8$ is hydrogen;

$R_9$ is hydrogen;

m is the integer 0

n is the integer 1.

15. The compound as recited in Claim 1, which is

N-[5-[[5-Ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide;

N-[5-[[5-Ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzamide;

N-[5-[[(4,5-Dimethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide;

N-[5-[[(5-t-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide;

N-[5-[[5-t-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trimethylacetamide;

N-[5-[[(4-Ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide;

N-[5-[[(5-*t*-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-N'-cyano-N"-(2,6-difluorophenyl)guanidine;

N-[5-[[(5-Isopropyl-2-oxazolyl)fluoromethyl]thio]-2-thiazolyl acetamide;

N-[5-[[(5-t-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl] aminophenyl-4-(2-hydroxyethyl)sulfonamide;

N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]aminophenyl-4-sulfonamide;

N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-4-aminopyrimidine;

N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-3-(hydroxymethyl)aniline;

N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-2-aminopyridine;

N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2- thiazolyl]-2-[5-[(((3-hydroxy-2,2-dimethyl)propyl)amino)methyl]] aminopyridine; or

a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition comprising a compound of Claim 1, in combination with a pharmaceutically acceptable carrier, and an anti-cancer agent formulated as a fixed dose.

18. A pharmaceutical composition comprising a compound of Claim 1, in combination with a pharmaceutically acceptable carrier, and a modulator of p53 transactivation formulated as a fixed dose.

19. A pharmaceutical composition according to claim 16, comprising a compound of Claim 1 in combination with a pharmaceutically acceptable carrier, with an anticancer treatment or anticancer agent administered in sequence.

20. The pharmaceutical composition according to Claim 18, wherein said combination comprising said compound of Claim 1 and said

pharmaceutically acceptable carrier, is administered prior to administration of said anticancer treatment or anticancer agent.

21. The pharmaceutical composition according to claim 18, wherein said combination comprising said compound of Claim 1 and said pharmaceutically acceptable carrier, is administered after administration of said anticancer treatment or anticancer agent.

22. A method of inhibiting protein kinases which comprises administering to a mammalian specie in need thereof an effective protein kinase inhibiting amount of a compound of Claim 1.

23. A method of inhibiting cyclin dependent kinases which comprises administering to a mammalian specie in need thereof an effective cyclin dependent kinase inhibiting amount of a compound of Claim 1.

24. A method of inhibiting cdc2 (cdk1) which comprises administering to a mammalian specie in need thereof an effective cdc2 inhibiting amount of a compound of Claim 1.

25. A method of inhibiting cdk2 which comprises administering to a mammalian specie in need thereof an effective cdk2 inhibiting amount of a compound of Claim 1.

26. A method of inhibiting cdk3 which comprises administering to a mammalian specie in need thereof an effective cdk3 inhibiting amount of a compound of Claim 1.

27. A method of inhibiting cdk4 which comprises administering to a mammalian specie in need thereof an effective cdk4 inhibiting amount of a compound of Claim 1.

28. A method of inhibiting cdk5 which comprises administering to a mammalian specie in need thereof an effective cdk5 inhibiting amount of a compound of Claim 1.

29. A method of inhibiting cdk6 which comprises administering to a mammalian specie in need thereof an effective cdk6 inhibiting amount of a compound of Claim 1.

30. A method of inhibiting cdk7 which comprises administering to a mammalian specie in need thereof an effective cdk7 inhibiting amount of a compound of Claim 1.

31. A method of inhibiting cdk8 which comprises administering to a mammalian specie in need thereof an effective cdk8 inhibiting amount of a compound of Claim 1.

32. A method for treating proliferative diseases comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

33. A method for treating cancer comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

34. A method for treating inflammation, inflamatory bowel disease, or transplantation rejection, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

35. A method for treating arthritis comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

36. A method for treating infection by HIV, or for treating and preventing the development of AIDS, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

37. A method for treating viral infections, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

38. A method for treating fungal infections, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

39. A method for preventing the development of cancer or tumor relapse, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

40. A method for treating neurodegenerative disease, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

41. A method for treating proliferative diseases comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 17.

42. A method for treating cancer comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 17.

43. A method for preventing the development of cancer or tumor relapse, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 17.

44. A method for treating proliferative diseases comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 18.

45. A method for treating cancer comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 18.

46. A method for preventing the development of cancer or tumor relapse, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 18.

# INTERNATIONAL SEARCH REPORT

Int    nal Application No
PCT/US 00/33037

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7 C07D277/54 C07D417/12 C07D417/14 A61K31/427 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, BEILSTEIN Data, WPI Data, EPO-Internal

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 99 24416 A (BRISTOL-MYERS SQUIBB COMPANY) 20 May 1999 (1999-05-20) the whole document | 1-46 |

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
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# INTERNATIONAL SEARCH REPORT

formation on patent family members

In  nal Application No
PCT/US 00/33037

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9924416 A | 20-05-1999 | AU 1295599 A | 31-05-1999 |
| | | BR 9814124 A | 03-10-2000 |
| | | EP 1042307 A | 11-10-2000 |
| | | NO 20002153 A | 11-05-2000 |
| | | US 6040321 A | 21-03-2000 |